REACTIONS OF EPOXIDES WITH NEIGHBOURING NUCLEOPHILES

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by

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CONTENTS

ABSTRACT

The syntheses and acid catalysed rearrangements of cis- and trans-3,4-epoxypentan-1-ols (28,22), 4,5-epoxyhexan-1-ols (30,24) and 5,6-epoxyheptan-1-ols (32,26) have been described. Isomerizations of these compounds gave cyclic ether derivatives as the major products. The 5,6-epoxyheptan-1-ols (32,26), which can form either a six- or a seven-membered oxide ring, were found to react to give six-membered ring products. With the 4,5-epoxyhexan-1-ols (30,24) the five-membered ring product was formed more readily than the six-membered one. Finally with the 3,4-epoxypentan-1-ols (28,22) the five membered ring product was formed in preference to the four-membered alternative.

For the cis- and trans-4,5-epoxyhexan-1-ols (30,24) and 5,6-epoxyheptan-1-ols (32,26) where the hydroxyl group can readily approach the rear of at least one carbon atom of the epoxide ring the products were formed via an A2 mechanism with complete inversion of stereochemistry. Steric hindrance to nucleophilic attack by the hydroxyl group at one of the epoxide carbon atoms of cis-4,5-epoxyhexan-1-ol (30) was found to reinforce the preference to form a five-membered ring product.

In the case of the cis- and trans-epoxypentan-1-ols (28,22) where approach of the hydroxyl group to the rear of the epoxide ring is more difficult, compounds involving retention as well as those of inversion of configuration were formed. These products have been rationalized in terms of an A1 mechanism.

The acid catalysed reactions of cis- and trans-3,4-epoxypentan-1-ol acetates (29,23), 4,5-epoxyhexan-1-ol acetates

(31,25) and 5,6-epoxyheptan-1-ol acetates (33,27) were also investigated. Isomerizations of cis- and trans-3,4-epoxypentan-1-ol acetates (29,33) and 4,5-epoxyhexan-1-ol acetates (31,25) but not 5,6-epoxyhexan-1-ol acetates gave cyclic ether derivatives having complete retention of configuration. These compounds are considered to form via ortho ester intermediates.

INTRODUCTION

Acid Catalysed Reactions of Epoxides

The chemistry of the epoxide group is dominated by the release of strain energy that occurs on ring opening. This ring strain has been calculated[1] to be 13 kcal.mole^{-1} and is relieved by reactions that may be catalysed by heat, acids, or bases. The most readily occurring and most widely studied of these are the acid catalysed reactions. When a Lewis, or strong proton acid coordinates with an epoxy-oxygen lone pair one of the C-O bonds of the epoxide ring is polarized and cleaved. This may be accompanied by a variety of processes of which the three most important are shown diagrammatically in Fig. 1.

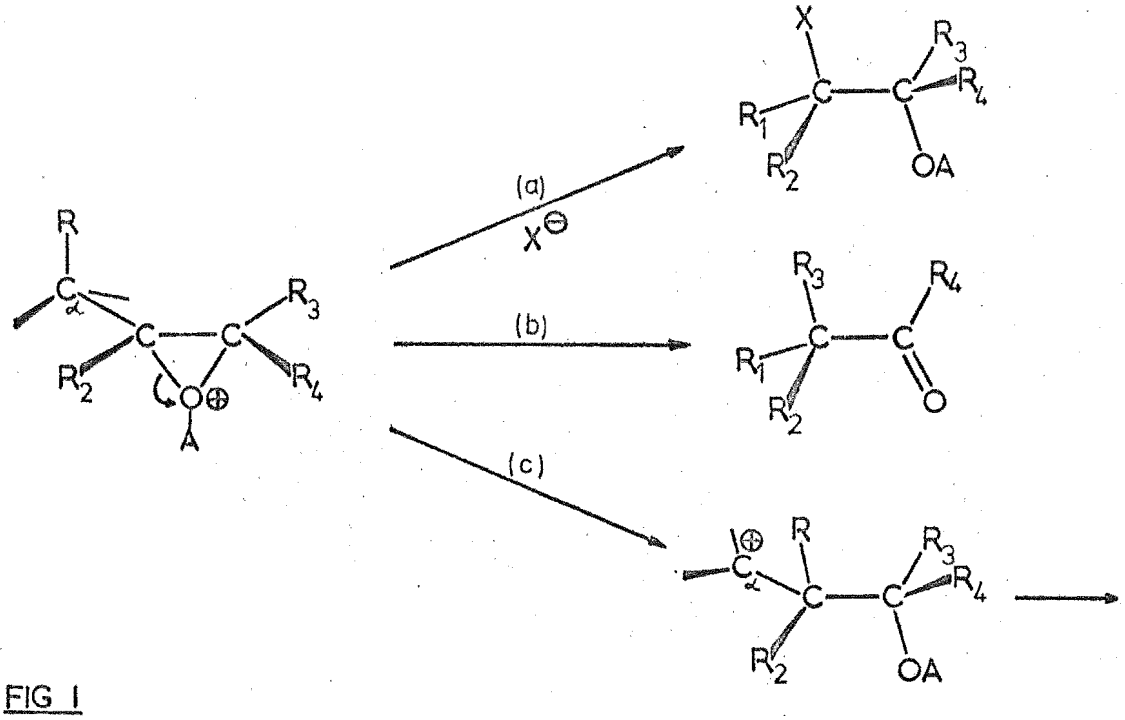

FIG 1

Process (a) occurs when there is attack by an external or conveniently placed internal nucleophile as the epoxide ring is being cleaved. A considerable variety of such reactions has been reported in the literature with fluoride ion[2-4], bonded

chlorine (C-Cl)[5], carbon-carbon double bonds[6], hydroxyl[7-9], carbonyl[10], and acetyl[11] groups being typical nucleophiles. The scheme shown in Fig. 2 representing acid catalysed alcoholysis of an epoxide, to give a product with inversion of configuration, is characteristic of this type of reaction.

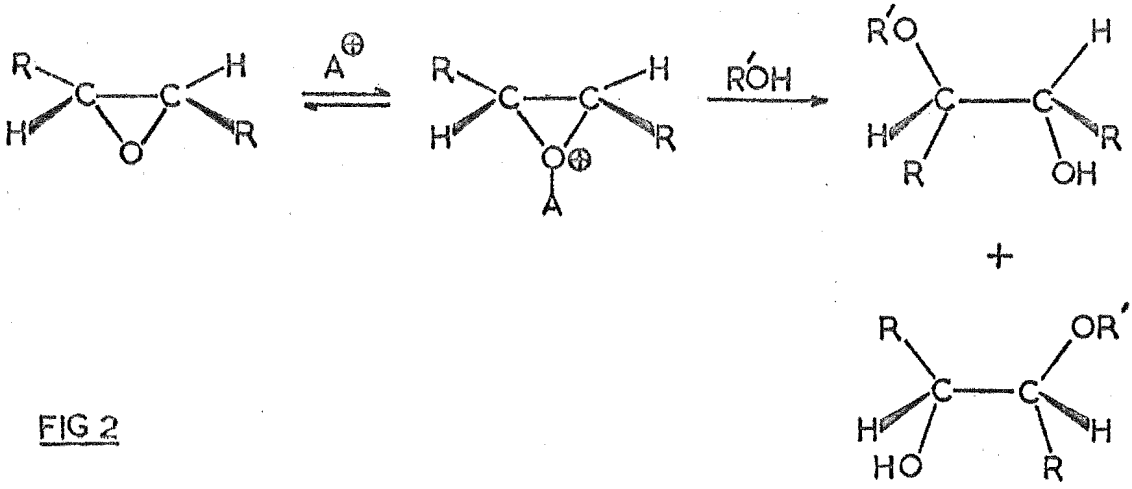

FIG 2

The strength of the attacking nucleophile and its availability play an important part in determining the course of the reaction. If no nucleophile is present the orientation of ring opening in epoxides is dependent on the combined electron releasing power of the substituents on each ring carbon[12], with opening being favoured at tertiary > secondary > primary centres. However, when nucleophiles are present during the acid catalysed reactions of epoxides, epoxide ring opening may occur at the least substituted centre. This happens because the least substituted epoxide carbon atom is also usually the sterically less hindered and thus more open to attack by the nucleophile. Examples of acid catalysed opening of epoxides in which the major product is formed from nucleophilic attack at the least substituted carbon atom are quite common[7,8].

Process (b) in Fig. 1 takes place when there is migration of a substituent from one carbon of the epoxide ring to the

other to give a carbonyl compound. This reaction pathway is greatly facilitated when the reaction is carried out in an inert solvent so that there are no competing reactions from more efficient external nucleophiles. There must, of course, be no good internal nucleophiles that have ready access to the epoxide ring or these will also react. If migration takes place the choice of substituents R_3 or R_4 (Fig. 1) is determined partly by their relative migratory aptitudes and partly by their steric environment. Migratory aptitudes follow the general trend aryl > acyl > hydrogen > alkyl[13], in all reactions involving 1,2-shifts to electron deficient centres. Examples of this type of process are numerous with a typical one being the rearrangement of trans-epoxybutane, Fig. 3.

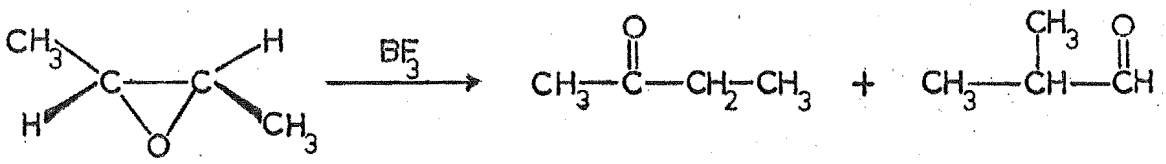

FIG 3

Hydride migration gives butanone whereas methyl migration gives methylpropanal. These rearrangements are usually carried out using a Lewis acid such as boron trifluoride. Judicious variation of solvent type and catalyst help to suppress the yields of products formed by other pathways.

An interesting feature of process (c) in Fig. 1 are the fragmentation reactions[3,14,15]. These reactions tend to occur when an epoxide is reacted with a Lewis acid in a non-participating solvent especially when the stereochemistry of the molecule is such that rearrangement via process (b) cannot readily occur. In the example shown in Fig. 4 hydride

migration is difficult as the conformation for this process involves serious steric interactions between two tert.-butyl groups or one tert.-butyl group and the boron trifluoride coordinated oxygen.

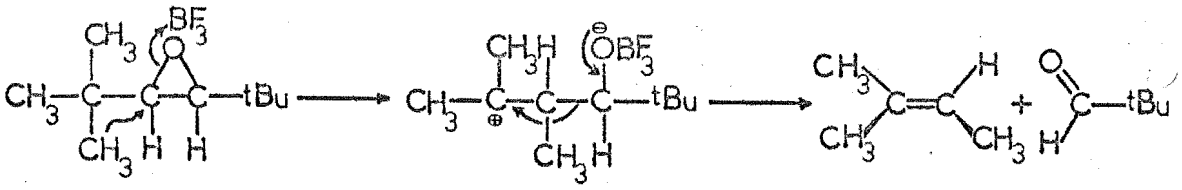

FIG 4

When this type of epoxide is treated with boron trifluoride in a basic solvent such as ether fluorohydrins are typical products[2].

(i) Mechanism of the Acid Catalysed Reaction of Epoxides with Nucleophiles

This discussion is concerned with process (a) (Fig. 1). Parker and Isaacs[60] consider that nucleophilic ring opening of epoxides under neutral or basic conditions produces a transition state in which bond breaking is greater than or equal to bond making. This means that in the former situation a small positive charge develops on the attacked carbon, while in the latter case the carbon atom remains neutral. If no charge develops on the carbon being attacked the mechamism is A2 while if some positive charge is generated the mechanism is considered to be "borderline A2". In the extreme case when no bond forming occurs the nucleophile does not participate in the rate-determining step (i.e. a free carbonium ion is formed) and the mechanism is designated as A1. The three different transition states considered above are represented diagrammatically in Fig. 5.

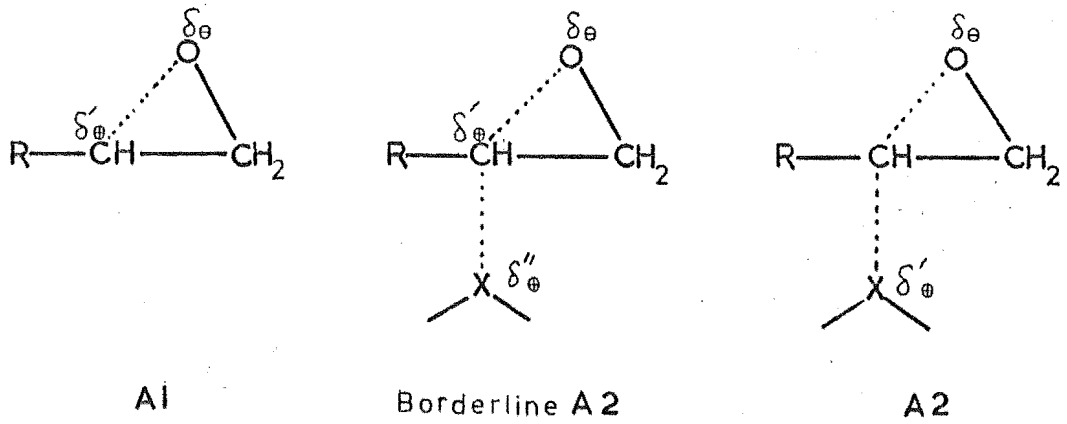

FIG 5

A study of the three transition states shows that the reactions proceeding via A2 and borderline A2 mechanisms give inversion of configuration while those going via an Al mechanism will give partial or complete racemization at the point of attack. Under conditions of acid catalysis the initial protonation or Lewis acid coordination of the epoxide oxygen atom* is likely to produce a transition state for ring opening in which bond breaking has progressed to a greater extend than that under neutral or basic conditions.

A considerable amount of research has been carried out on the acid catalysed reactions of epoxides by nucleophiles and the literature[7,16] divides them into two classes, "normal" and "abnormal"**. With normal attack the nucleophile approaches the least substituted carbon of the epoxide ring, while abnormal attack occurs when the nucleophile approaches the more substituted carbon.

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* It is now generally accepted that the initial protonation or Lewis acid coordination is a fast, reversible step, the rate limiting step being the reaction of the complex with the nucleophile.

** The terminology used is a legacy from work on the neutral or base catalysed reactions of epoxides with nucleophiles where attack is much more specific for the unhindered site.

The various experimental methods and criteria by which elucidation of the reaction mechanisms have been attempted are outlined briefly below. Long et al.[17] studied the kinetics and product compositions for the acid catalysed hydrolysis of alkyl substituted epoxides. From the correlation between the rate constants and the acidity function, H_0, Pritchard and Long[18] concluded that the reaction proceeded via the A1 mechanism. It appears unwise however, to place too much weight on such correlations[19], and in his later review Long himself discounted his earlier conclusion[20].

A second criterion for mechanism used by Pritchard and Long[18] was the application of the limiting form of the Taft equation to the rate data for substituted epoxides. In this form the Taft equation is $\log k/k_0 = \sigma^*\rho^*$, where k and k_0 are the rate coefficients for the reactions of the substituted epoxide and epoxypropane respectively, σ^* is the substituent constant and ρ^* is the reaction constant. They obtained a value of -1.95 for ρ^* and interpreted this as indicating an A1 mechanism. Parker and Isaacs[12] suggested that this need not necessarily be correct for two reasons. The negative value of ρ^* indicates that the reaction is facilitated by electron-releasing substituents which, by increasing the electron density on the oxygen atom of the epoxide, increase the amount of epoxide conjugate acid produced in the initial equilibrium and therefore increase the overall rates in both the A1 and the A2 mechanism. Also, a negative value of ρ^* can be accommodated by a "borderline A2"[12] mechanism, Fig. 5.

A third criterion depends on the assumption that the rates of A1 and A2 hydrolysis are affected differently by the substitution of deuterium oxide for water. The values of the

ratio of second-order rate coefficients for hydrolysis of epoxides in deuterium oxide and in water obtained by Pritchard and Long[21] were taken to indicate an Al mechanism; in a more detailed analysis Swain and Thornton[22] have argued that these reports are more reasonably interpreted by a borderline A2 mechanism.

A fourth criterion for differentiating between the mechanisms by which acid catalysed nucleophilic attack of epoxides occur is the value of the entropy of activation. In the case of an A2 mechanism the transition state must be very ordered and so a low entropy of activation would be expected. With an Al mechanism however, the nucleophile does not enter as the oxygen leaves and so the transition state would be much less ordered than in the previous case. Literature values of entropies of activation for esterification of carboxylic acids in an alcohol solvent, which are regarded as proceeding *via* an A2 mechanism, vary from -35.7 cal.mole^{-1}K^{-1} for acetic acid in ethanol[23] to -17.0 cal.mole^{-1}K^{-1} for phenylacetic acid with methanol[7]. The values of entropy of activation for the solvolysis of compounds regarded as reacting *via* an Al mechanism in an alcohol solvent vary from +0.79 cal.mole^{-1}K^{-1} for *tert*. butyl iodide in 4:1 ethanol-water[24] to -7.4 cal.mole^{-1} K^{-1} for *tert*. butyl bromide in ethanol[25].

Chapman *et al*.[7] have studied the acid catalysed alcoholysis of monosubstituted epoxides and obtained both normal and abnormal products. The entropies of activation for methanolysis in the normal position were approximately -17 cal.mole^{-1}K^{-1} and these results were interpreted in terms of an A2 mechanism. Methanolysis of the epoxides in the abnormal position gave entropies of activation in the region

of -14 cal.mole^{-1}K^{-1} and these were interpreted in terms of a borderline A2 mechanism. In many of the reactions that Chapman et al. have regarded as proceeding by a borderline A2 mechanism on the grounds of entropies of activation, there is evidence for considerable charge separation in the transition state. This evidence includes: - (i) the Hammett ρ values (-3.8 to -4.2)* obtained for abnormal attack on substituted (1,2-epoxyethyl) benzenes, (ii) the presence of 11% of product of retention of configuration in the reaction of D(+)-(1,2-epoxyethyl) benzene, Fig. 6, (iii) the ρ* value (-1.3) for abnormal attack on substituted epoxypropanes.

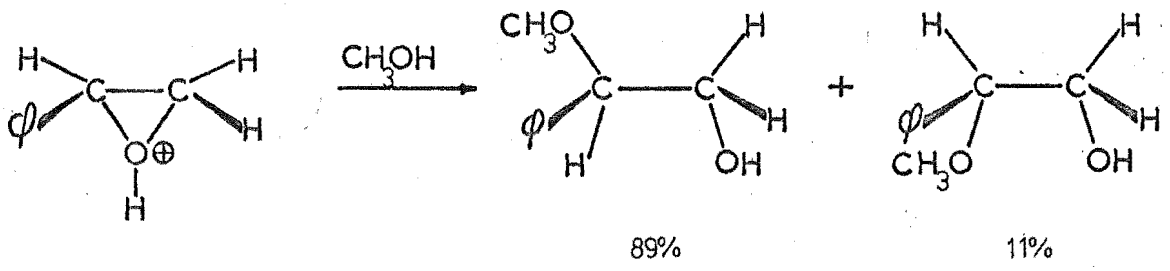

FIG 6

Chapman and his co-workers rearranged only one epoxide that contained a tertiary carbon atom, 1,1-diphenylepoxyethane, and the entropy of activation was such (-0.6 cal.mole^{-1}K^{-1}) that they considered the reaction to proceed by an A1 or possibly borderline A1 mechanism.

Stereochemical evidence for the mechanism of the acid catalysed reaction of alkyl substituted epoxides with nucleophiles is comparatively straightforward. When the attacking nucleophile is readily available the reactions follow an A2 or borderline A2 mechanism and exclusive inversion of configuration results[27], Fig. 2. However, if the nucleophile is not available for backside attack on the epoxide the reaction may, at least in the case of epoxides with a tertiary

*The solvolysis of α,α-dimethylbenzyl chlorides to give benzyl carbonium ions has ρ values of -4.43 to -4.82[26].

carbon, proceed through an Al mechanism. An example of this type of reaction is the rearrangement of 8α,20-epoxymanöol and 8β,20-epoxymanöol[29] by toluene-p-sulphonic acid in benzene. In the case of the α-epoxide backside attack by the hydroxyl group is possible and the expected six membered cyclic ether is formed in 20% yield, Fig. 7. With the β-epoxide backside approach by the hydroxyl group is impossible because of steric reasons and yet the same cyclic ether as formed from the α-epoxide is produced in 20% yield. This means that a free carbonium ion is probably formed at the 8- position and is attacked by the hydroxyl group to give the required product, Fig. 7.

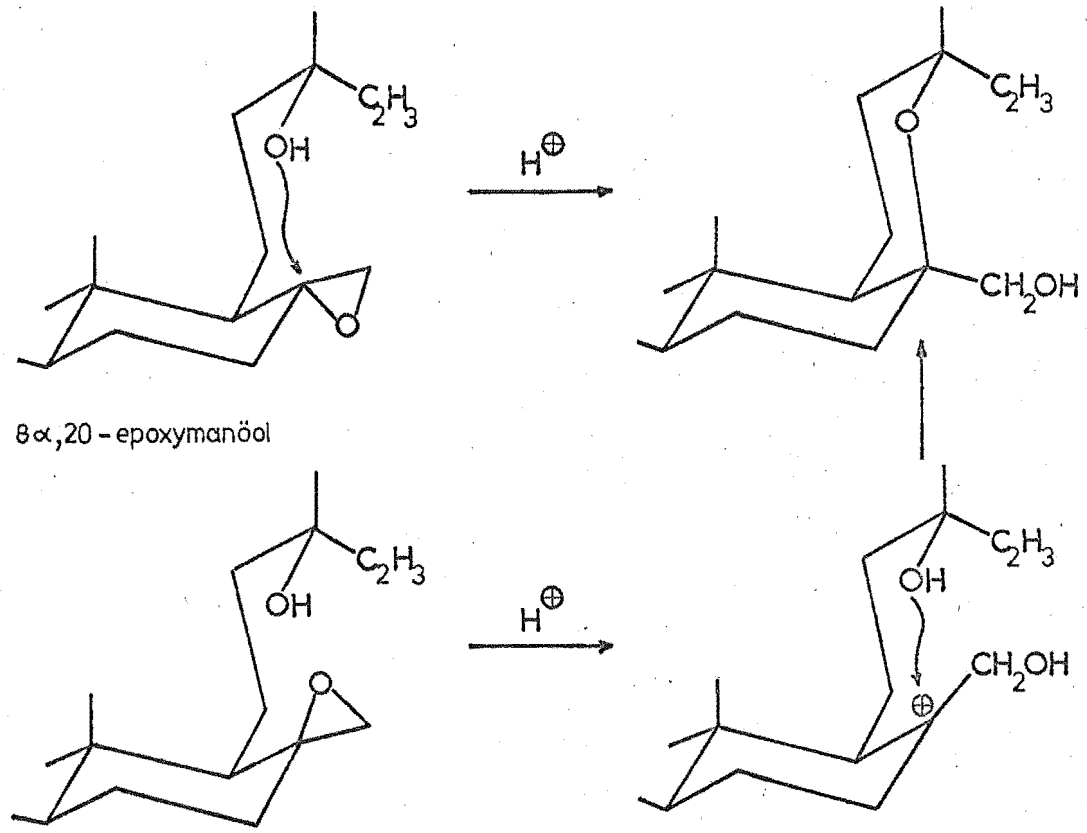

FIG 7

Complete or partial retention of configuration has been observed for the acid catalysed nucleophilic substitution of a large number of epoxides (asymmetric at both carbons) with

π-electron donating substituents[28]. The most probable mechanism is initial protonation of the epoxide, and ring opening to give an ion-pair within a 'solvent cage', followed by rapid attack by the anion on the benzyl (or allyl) carbonium ion, Fig. 8. Retention is favoured by the use of non-polar solvents, acids whose conjugate bases are strongly nucleophilic (e.g. CX_3CO_2H, X = halogen) and a trans-disposition of the most bulky epoxide substituents.

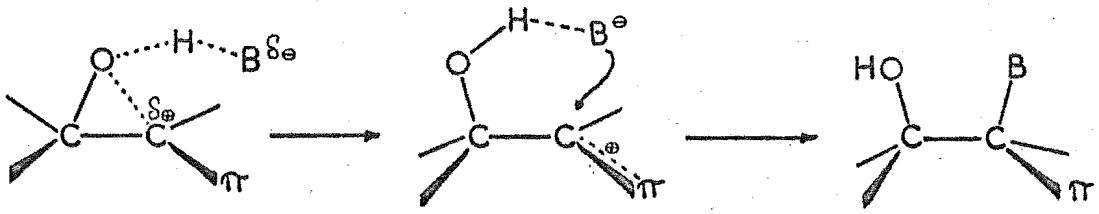

FIG 8

From the evidence presented above the acid catalysed reactions of epoxides containing alkyl and other non-π-bonding substituents with readily available nucleophiles appear almost certain to proceed via A2 or borderline A2 mechanisms. The mechanism by which aryl substituted epoxides rearrange seems to be much more open to controversy.

(ii) Ring Formation by Acid Catalysed Intramolecular Nucleophilic Attack of Epoxides

It was demonstrated in the previous section that during the acid catalysed reaction of epoxides a nucleophile may attack at either of the two carbon atoms of the epoxide ring. The orientation of epoxide ring opening was shown to be dependent on such factors as the strength of the nucleophile, the combined electron releasing power of the substituents, and the relative steric hindrance to attack by the nucleophile at the two carbon atoms. When the attacking nucleophile is

part of the same molecule as the epoxide function a cyclic product will result and the ease with which the new ring can form will then play a large part in the orientation of the opening of the epoxide.

Ease of ring formation is not synonymous with ring stability. Whereas the activation energy for ring closure might be expected to reflect the stability of the ring formed to some extent, other factors are important. The most significant of these involves the probability of having the ends of the ring forming chain approach each other. This probability decreases as the ring size increases and reflects itself in an unfavourable entropy of activation for the formation of medium and large rings. The overall ease of ring closure may thus be derived from two factors: a steady decrease in the ease with which the ends of the chain meet and form the ring, and a strain factor which becomes more favourable to closure as the ring size increases from three- to six-membered, and then less favourable as it increases further up to nine-membered, and then more favourable again for larger rings. Overall the ease of ring formation is relatively high for three-membered rings because of the high probability factor as three atoms are necessarily in the optimum position for ring formation. It drops sharply for the four-membered ring but rises quickly again for the five-membered ring because of the considerable reduction in the strain factor. The ease of formation of a six-membered ring is less than for a five-membered one because the slight improvement in the strain factor is outweighed by a deterioration in the distance factor. There is a sharper drop for the seven-membered ring as both strain and distance factors become worse. Eight-membered

rings are even more difficult to form than seven-membered ones as non-classical strain* sets in in the former case as in the nine- and ten-membered rings.

The effect of alkyl substituents, especially gem-dialkyl, on the chain that is to form part of a ring structure is to favour the formation of a cyclic compound. Ingold and Thorpe[54] suggested that the diminution of the internal angle in a small ring (e.g. to 60° in cyclopropane) leads to a spreading apart of the external angle. This relieves the steric compression between substituents attached to the same carbon, thus favouring the ring form over the open chain form, Fig. 9a. This explanation is probably correct for small rings. However in common rings[56] (five-, six-, and seven-membered rings) with their normal or nearly normal bond angles the theory fails to explain the enhanced ring stability.

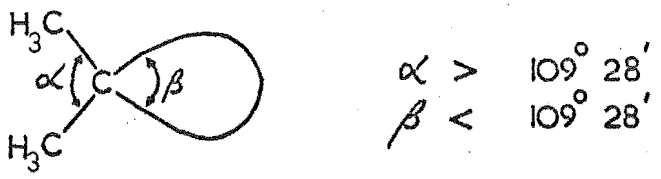

FIG 9a

A theory of the "gem-dialkyl effect" which appears to be applicable at least in the case of six-membered rings, has been proposed[55] in terms of the enthalpies and entropies of open-chain versus ring compounds. Analysis of a number of specific cases of substituted hexanes on one hand and

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* The total strain in medium sized rings has been termed[52] "non-classical strain" to distinguish it from classical or angle strain. Although this term is widely used it is a misnomer, inasmuch as it is now known[53] that angle strain is sometimes a substantial part of the total strain in medium-sized rings. "Non-classical strain" is actually a composite of torsional, angle, and transannular strain.

substituted cyclohexanes on the other discloses that there are fewer extra gauche interactions due to the alkyl substituents in the rings than there are in the open chains. This means that, compared with an unsubstituted chain, the substituted chain has a more favourable enthalpy of ring closure. An example of this effect occurs in the gem-dimethyl substituted straight-chain hexanes and cyclohexanes. When n-hexane is in its most stable conformation there are no gauche interactions but, when ring closure to cyclohexane takes place six gauche interactions are introduced. On the other hand, 3,3-dimethyl-hexane has four gauche interactions in the most stable conformation whereas gem-dimethylcyclohexane has eight. This means that the cyclization of the disubstituted compound is favoured over that of the non-substituted compound by two gauche interactions, or approximately 1.6 k cal.mole^{-1}, Fig. 9b.

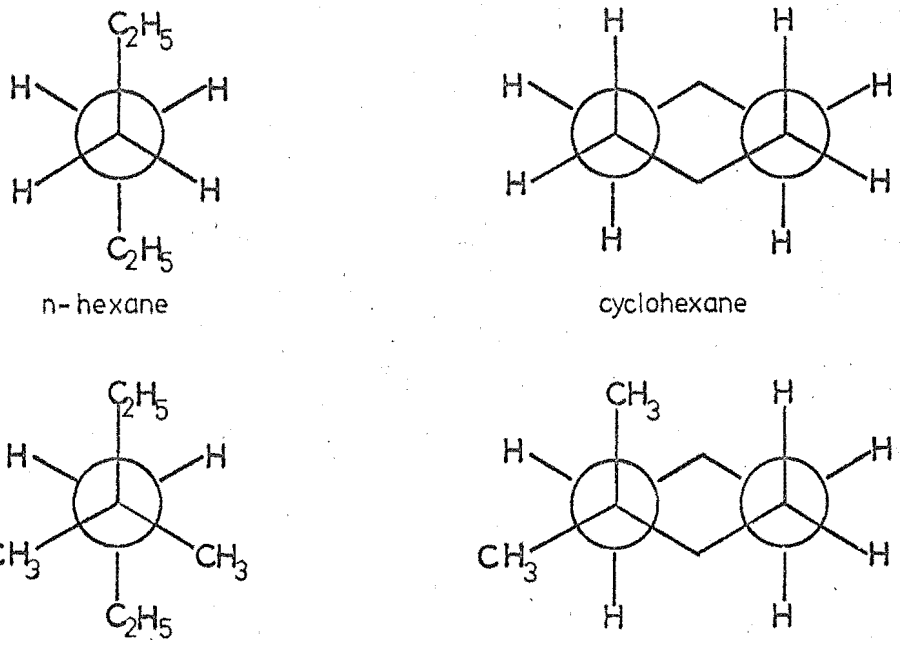


FIG 9b

In addition there is an entropy effect due to branching based on the fact that branching reduces the rotational entropy of open-chain compounds. Branching cannot reduce the entropy of the ring compound very much because it has little freedom of internal rotation to begin with. Thus the entropy factor also favours ring closure for the more branched compounds. Since branching both reduces the enthalpy and increases the entropy

of ring closure, it decreases the free energy of ring closure and leads to an equilibrium more favourable to the ring structure.

If new three-membered rings were formed by the acid catalysed nucleophilic attack of epoxides they would probably have only a fleeting existence because of their inherent instability under the acidic reaction conditions, however, four-membered ring products have been reported[11]. The most likely ring size of the products is that of the common rings. If the structure of the epoxide molecule is such that it is not possible to form common rings, a competing process such as isomerization to carbonyl compounds may become dominant.

In order to obtain good yields of cyclic compounds from the acid catalysed attack of epoxides by internal nucleophiles it is often necessary to operate in very dilute solution in order to avoid linear polymerization of the bifunctional molecules[57]. This dilution principle is based on the fact that the rate of an intramolecular ring closure generally depends on the first power of the substrate concentration, whereas the rate of intermolecular dimerization is proportional to the square of the concentration of the substrate.

(iii) Mechanism of Acid Catalysed Rearrangement of Epoxides to Give Carbonyl Compounds

The acid catalysed rearrangement of epoxides to give carbonyl compounds is shown in process (b) of Fig. 1. These rearrangements take place most readily when external nucleophiles are absent or not readily available. The reactions are usually catalysed by Lewis acids such as boron trifluoride or magnesium bromide but they may also be brought about by the action of heat alone. Parker and Isaacs[53] have postulated that the rearrangement must follow either:

(i) a one step "concerted" pathway in which bond breaking is

more important than bond making, Fig. 10(a), or

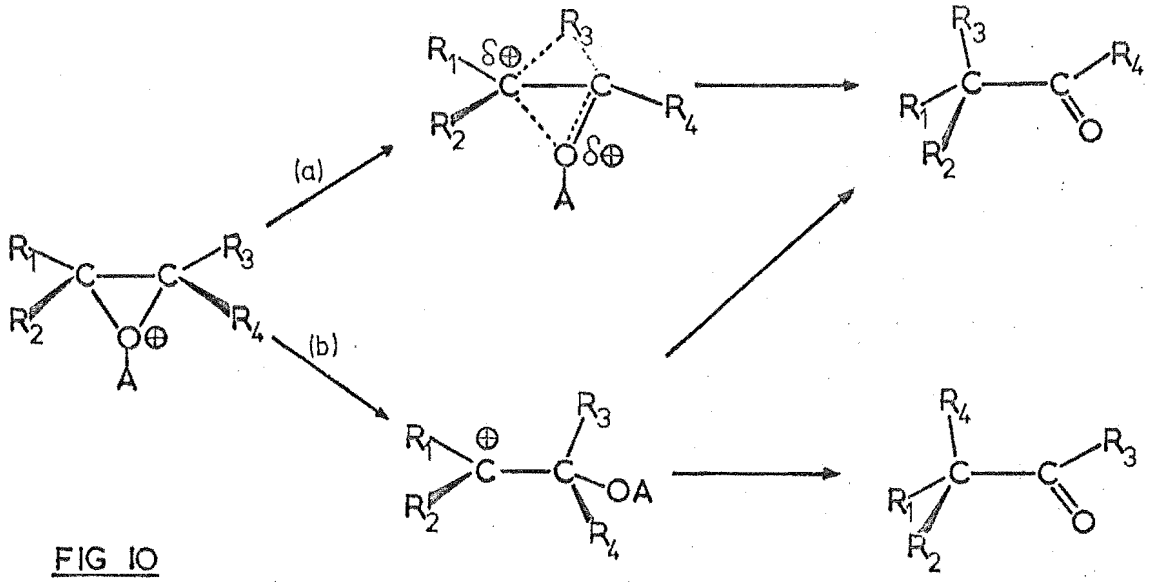


FIG 10

(ii) a two-step pathway in which the rate determining step leads to a discrete carbonium ion, Fig. 10(b). However, if the rearrangement is carried out by a Lewis acid such as boron trifluoride or magnesium bromide a fluorohydrin[2] or bromohydrin[30] intermediate may be formed, Fig. 11.

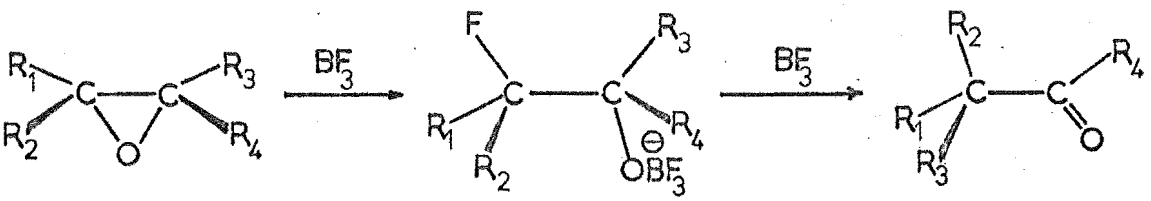


FIG 11

Further reaction of the halohydrin intermediate with the Lewis acid may give the products by a concerted pathway or by the two step mechanism.

As in the case of the acid catalysed nucleophilic attack of epoxides, rearrangements to give carbonyl compounds by concerted processes form products in which inversion has occurred whereas rearrangements <u>via</u> carbonium ions give partially or completely racemized products. If the isomerization of the epoxide proceeds by two concerted reactions <u>via</u> a

halohydrin intermediate then a product with complete retention is formed, Fig. 11. However, if the concerted and the double inversion rearrangements are of similar energy a mixture of products will be expected. This means that it is often extremely difficult to differentiate between rearrangements proceeding by concerted pathways and those involving carbonium ions by stereochemical data as both may give mixtures of products.

The difference between a concerted mechanism and a carbonium ion mechanism amounts to a question of whether the migrating substituent assists in the removal of the leaving group. It appears that distinguishing between the mechanisms for the acid catalysed isomerizations of epoxides is even more difficult than in the case of acid catalysed nucleophilic attack. The amount of carbonium ion character developed during the rearrangement of epoxides appears to vary over a considerable range depending on the number of substituents and their type. The effect of these substituents is discussed in more detail below.

Rearrangements of epoxides containing a tertiary carbon atom

In the case of tertiary epoxides strong evidence for the existence of discrete carbonium ions has been found. Blackett et al.[31] found that the α- and β-epoxides of 3-(66), 6-(67) and 7-(68) methylene cholestanes gave mixtures of the corresponding epimeric aldehydes with a bias towards that expected from a concerted rearrangement process. They consider that the data suggest a mechanism involving complete carbonium ion formation, Fig. 12, with the stereochemistry of hydride migration "loaded" in favour of top-side migration for the α-epoxides

and bottom-side migration for the β-epoxides.

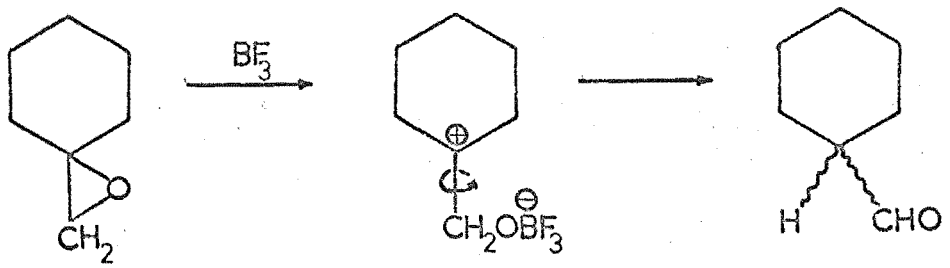


FIG 12

Later work[32], in which the rearrangement of 2,3,3-trimethyl-epoxybutane and both its stereospecifically C-1 monodeuterated derivatives were carried out in a non-participating solvent, established the comparability of the rate constant for a hydride shift k_{H_a} or k_{H_b} – 1.71 to that of the conformational change k^1, k^{-1} – 1.84, Fig. 13.

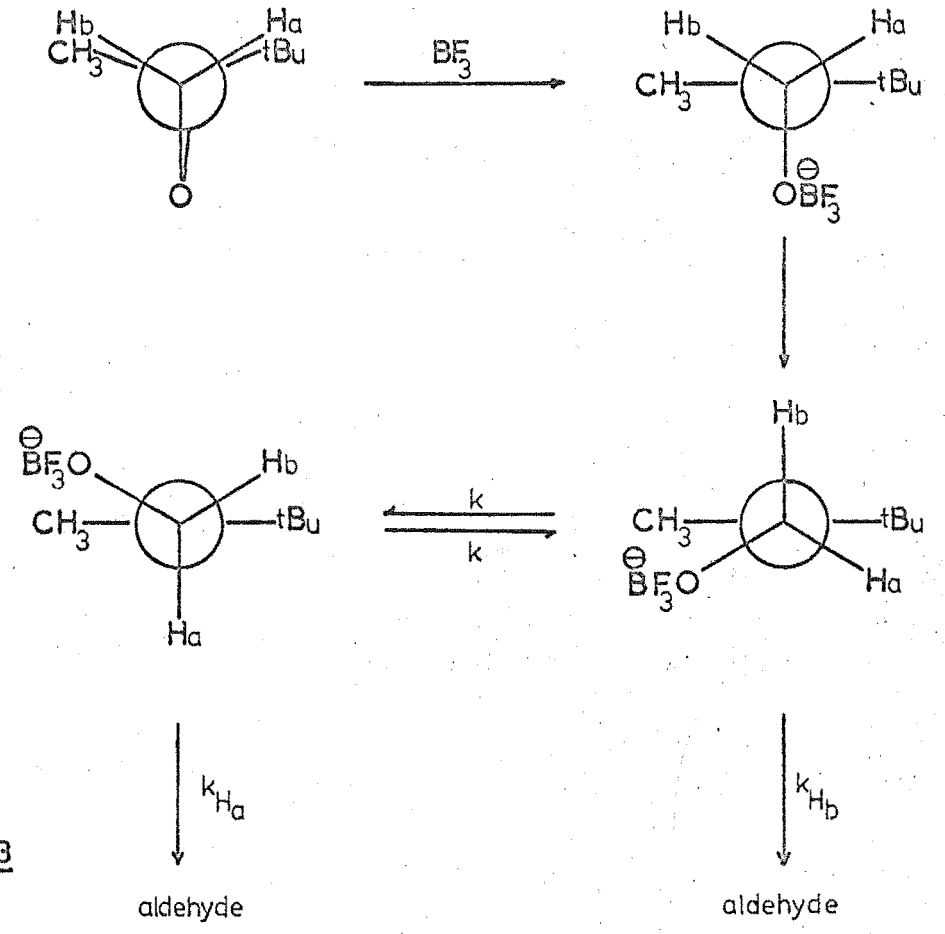


FIG 13

In contrast to the above results, when the two stereo-isomers shown in Fig. 14 are rearranged using boron trifluoride as a Lewis acid, different products are obtained[33].

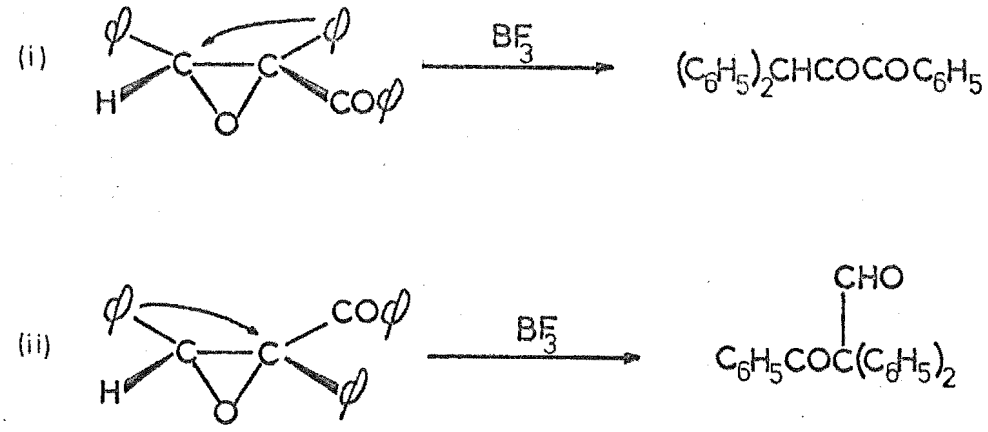


FIG 14

Parker and Isaacs[58] have considered this to be proof of a concerted mechanism and argue that if the reaction occurred *via* a carbonium ion both compounds would give the same product. However, if the reactions proceed by a concerted mechanism steric effects become important. Neither of the transition states for the concerted processes of the above reactions involves unfavourable *cis*-orientation of bulky groups, as can be seen in Fig. 15.

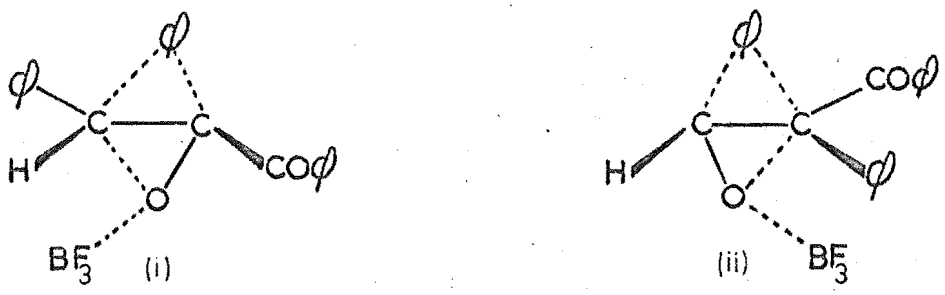


FIG 15

Such unfavourable *cis*-orientation (for example of a phenyl and a benzoyl group) would necessarily occur in one case if both epoxides rearranged to the same product. Recently Blackett[34]

has argued against this point of view and has stated that the steric effects are such that they strongly influence which aryl group can conjugate with the carbonium ion formed. He has examined space filling models of (a) and (b) and considers the ϕ_α is forced out of the plane of an incipient carbonium ion at C_α in epoxide (a), but may lie almost in this plane in epoxide (b), Fig. 16. Formation of a carbonium ion would therefore be favoured at C_β in (a) and C_α in (b). Rearrangement of these two intermediates then gives the observed products.

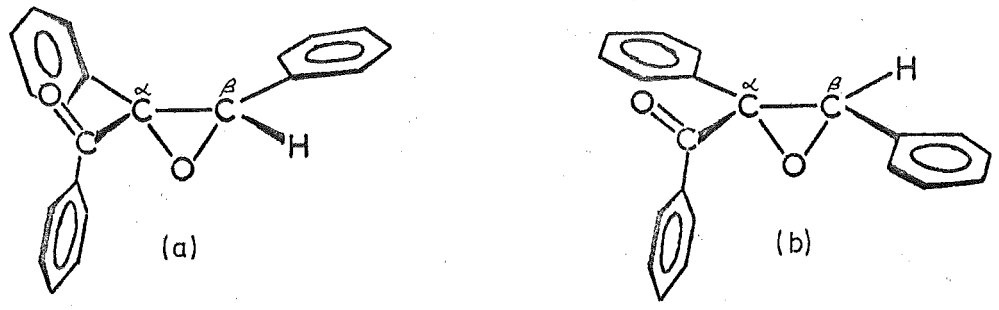


FIG 16

Rearrangements of epoxides containing secondary or primary carbon atoms

The acid catalysed rearrangements of cis- and trans-epoxybutanes have been observed[3,30,35] to give different product ratios in a manner paralleling the pinacol-pinacolone isomerization of the meso- and dl-isomers of butane-2,3-diol[35], Table 1. The data given in the table shows that methyl migration is more favoured in the rearrangement of trans-epoxybutane and meso-butane-2,3-diol than in the rearrangement of cis-epoxybutane and dl-butane-2,3-diol.

Table 1

Substrate	Reaction conditions	As percentage of total carbonyl product		Carbonyl product as percentage total yield
		ketone	aldehyde	
cis-2,3-epoxy-butane	BF_3OEt_2/ether	100	0	13
trans- "	"	84	16	12
cis- "	"	100	0	60
trans- "	"	75	25	60
cis- "	H_3PO_4(70%,aq)	93	7	37-58
trans- "	"	75	25	35-44
cis- "	$MgBr_2$/ether	100	0	75
trans- "		100	0	62
dl-butane-2,3-diol	H_3PO_4(70%,aq)	99-94	1-6	31-59
meso- "	"	79-71	21-29	37-71

House[30] has shown that the isomerization of the 2,3-epoxybutane isomers on treatment with magnesium bromide proceeds *via* bromohydrin intermediates. As the Lewis acid coordinated bromine is a relatively poor leaving group the isomerization products are dominated by migratory aptitudes rather than by torsional effects and so only butanone is formed. A similar mechanism for the rearrangement of the same epoxides by boron trifluoride is possible in which the *erythro*- and *threo*- fluorohydrins formed from the *cis*- and *trans*-epoxybutanes respectively could react further with boron trifluoride to give the required products. The different product ratios from the stereoisomers can be rationalized in terms of the fluorine being a good leaving group. This means

that the products formed are dependent on a balance of methyl and hydride migratory aptitudes and torsional strains between methyl groups and between methyl and hydroxyl groups, Fig. 17. From the diagram it may be seen that the torsional strain favours methyl over hydride migration in the reaction of threo-2-fluorobutan-3-ol with boron trifluoride but favours neither in the case of erythro-2-fluorobutan-3-ol.

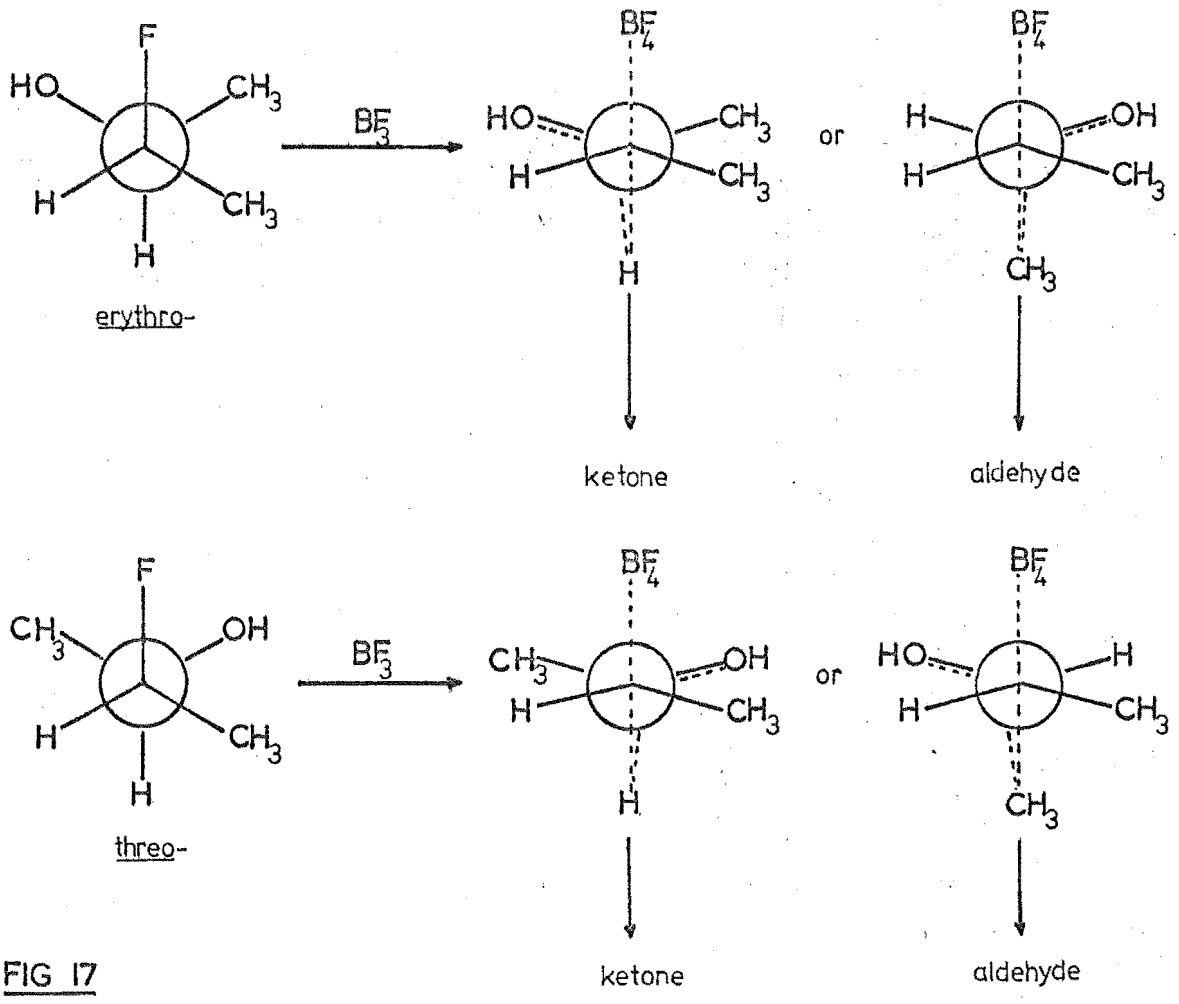


FIG 17

The major argument against such a mechanism is that the fluorohydrins would have to be formed with retention of configuration at one of the epoxide carbon atoms. So far all the fluorohydrins reported in the literature that are products from the reaction of BF_3-etherate with alkyl substituted epoxides have been formed with inversion of configuration at an epoxide carbon.

Although it has been shown that the lifetime of a tertiary carbonium ion formed by Lewis acid catalysed ring opening of an epoxide is of the order of time taken for a conformational change, these results were obtained using a non-polar solvent[32]. Thus although a secondary carbonium ion is inherently less stable than a tertiary one, if the former type of cation were generated from an epoxide in a basic solvent such as ether solvation, with resultant stabilization, of the positive charge would be expected to occur[62].

The products and product ratios obtained from the BF_3-etherate catalysed isomerizations of cis- and trans-epoxybutane can be rationalized in terms of secondary carbonium ion intermediates if the following two assumptions were made:

(a) torsional strains in the carbonium ion intermediates influence what products will form by making some conformations less favourable for nucleophilic attack (in this case hydride or alkyl migration) than others;

(b) the energy of activation for hydride or alkyl migration is small, or comparable, with the energies of conformational changes involving rotation about the C2-C3 bond of the carbonium ion, i.e. rapid hydride or alkyl migration tends to occur in the first attainable conformation of the carbonium ion where such attack is stereochemically possible.

Once a C3 carbonium ion is formed from trans- or cis-epoxybutane the C2 atom can rotate in a clockwise or anticlockwise direction, Figs 18,19. In the case of the carbonium ion formed from the trans-epoxybutane (Fig. 18(a)) clockwise rotation (i) places the methyl group in a position to migrate, and if such migration were to take place torsional interactions

would be kept to a minimum. If rotation of the C2 atom were to occur in an anticlockwise direction (Fig. 18 (ii)) the hydride group would be placed in a position to migrate. However, in such a conformation torsional strain between the Lewis acid coordinated oxygen and the methyl group is introduced. This interaction increases rapidly as hydride migration takes place and so such a process would not be favoured.

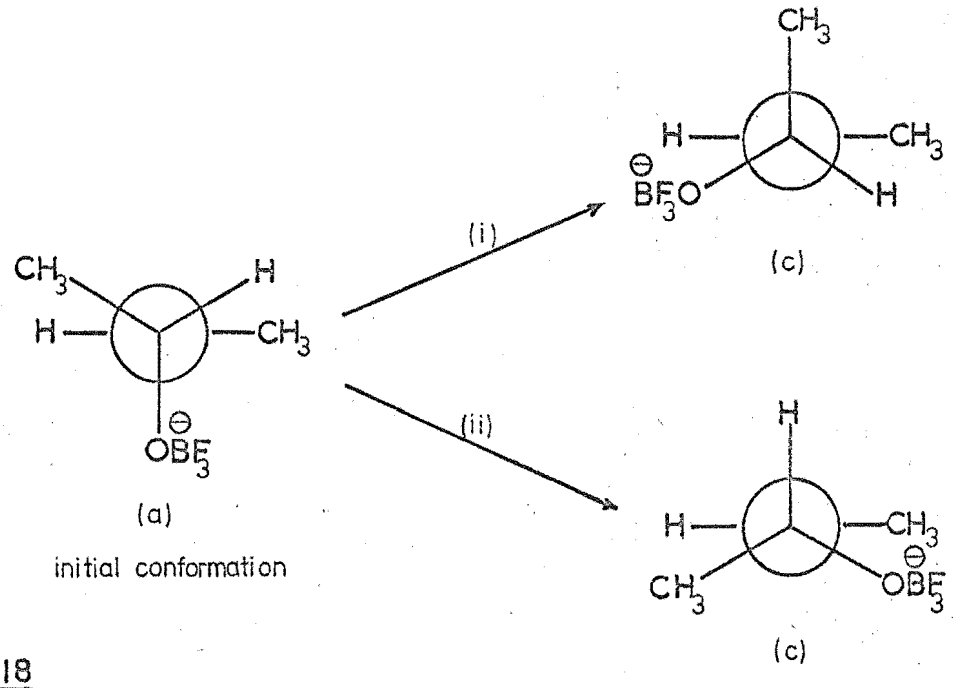


FIG 18

On the basis of torsional strains alone the major product from the rearrangement of trans-epoxybutane should be methyl propanal rather than butanone. However, the fact that the hydride group has a greater migratory aptitude than the methyl group would tend to favour the formation of butanone and so the actual product ratio is a compromise between these two effects.

Once a C3 carbonium ion is formed from cis-epoxybutane (Fig. 19(a)) methyl-methyl eclipsing must be overcome before clockwise rotation (i) of C2 can position the hydride group in

a conformation (c) where migration can take place. However, in such a position there is torsional strain between the methyl group and the Lewis acid coordinated oxygen atom. This interaction rapidly increases if methyl migration takes place.

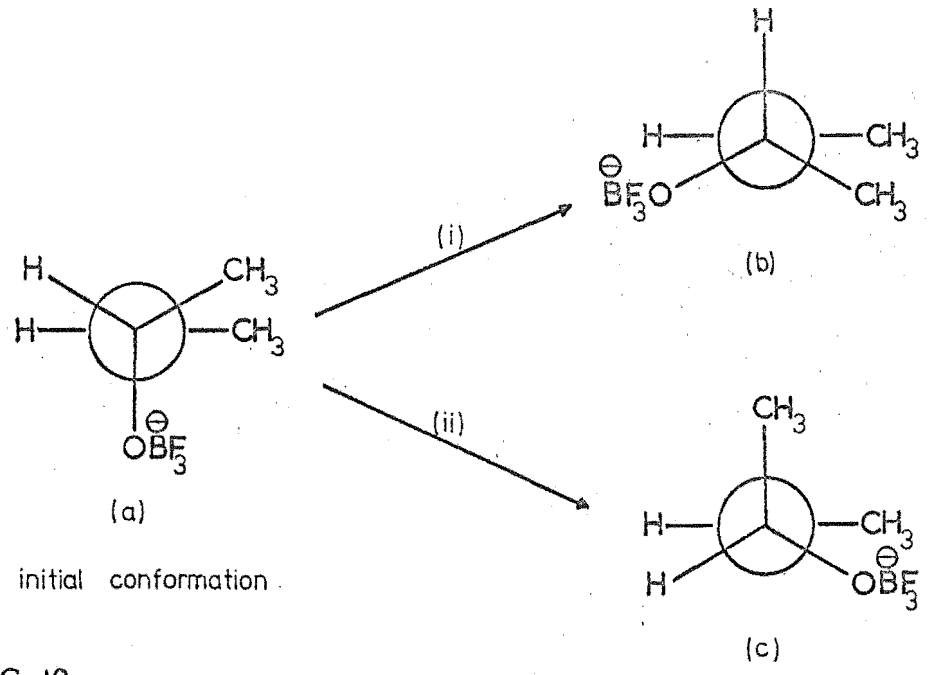


FIG 19

As both methyl and hydride migration in the carbonium ion intermediate formed from cis-3,4-epoxypentan-1-ol involve torsional strain between two reasonably large groups the products formed are dominated by the migratory aptitudes of the substituents. Thus butanone would be expected to be the major product because the hydride group has a greater migratory aptitude than the methyl group.

A third mechanism which does not involve an intermediate, such as a fluorohydrin or carbonium ion, can also explain the preference for methyl migration during the rearrangement of trans- as compared to cis-epoxybutanes. The two epoxybutanes may each form two transition states by a concerted pathway. These transition states are represented diagrammatically in Figs 20, 21.

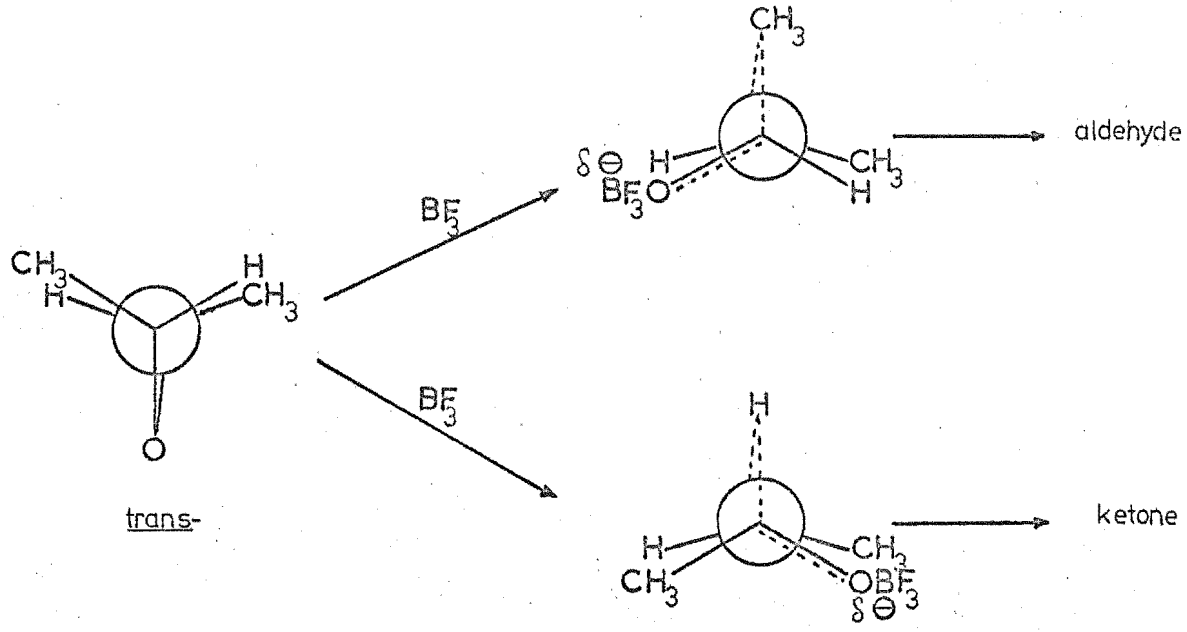


FIG 20

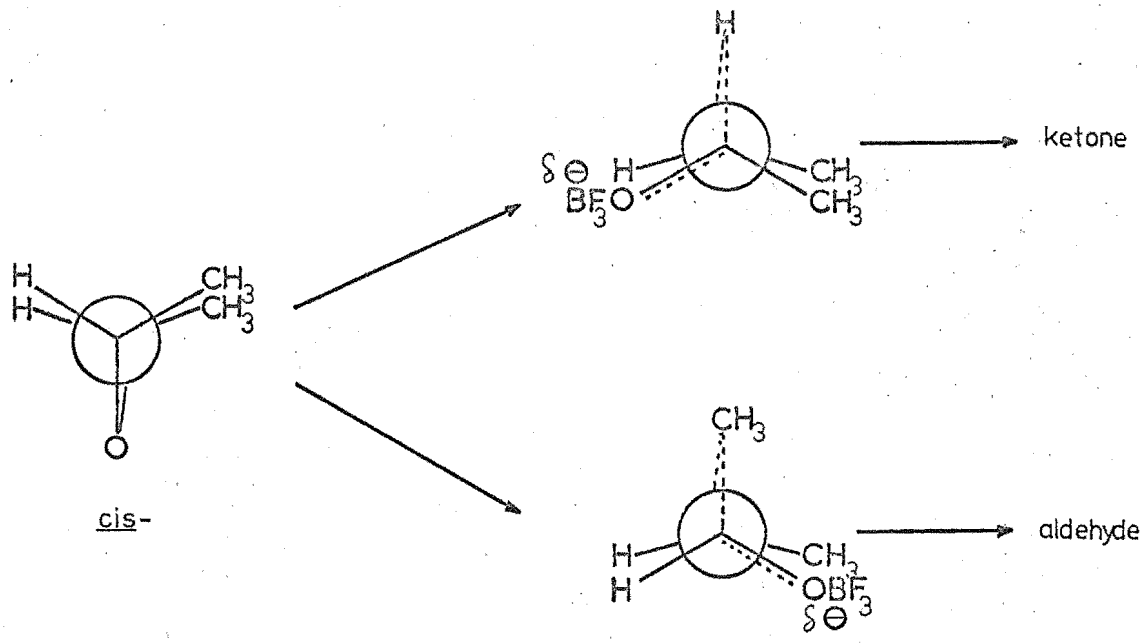


FIG 21

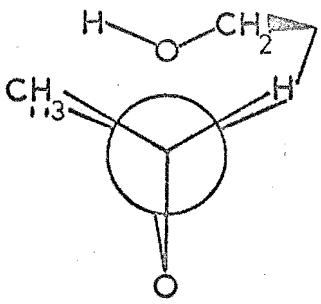
As in the previous argument, the products obtained from trans-epoxybutane will be a compromise between migratory aptitudes and torsional strain while those formed from cis-epoxybutane will depend mainly on migratory aptitudes.

The evidence presented in the literature suggests that the acid opening of epoxides at normal tertiary and possibly at aryl substituted secondary centres gives rise to discrete carbonium ion intermediates. Rearrangements involving opening at less stabilized centres may be concerted processes or may follow other pathways.

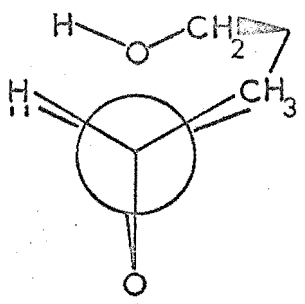
Objectives and Work Undertaken

The aim of this thesis was the systematic study of the acid catalysed reactions of epoxide molecules that contained nucleophiles. It was hoped that the nucleophile would be involved in the reaction and thus formation of cyclic products would be observed. The size of the ring formed and its stereochemistry should provide considerable information on the mechanism of the reaction.

The cis- and trans-isomers of 3,4-epoxypentan-1-ol (28,22), 4,5-epoxyhexan-1-ol (30,24) and 5,6-epoxyheptan-1-ol (32,26) were chosen for investigation for several reasons. The molecules are small and simple and therefore it should be relatively easy to pinpoint the effects that cause changes in products or product ratios. As the hydroxyl group is a good nucleophile, cyclic reaction products should be formed in good yield without having to resort to adding gem-dialkyl substituents to the carbon chain to assist ring closure. If, during the acid catalysed opening of the epoxide, the hydroxyl group were to attack the ring carbon atom furthest from the alcohol function there would be a much greater steric hindrance to nucleophile approach by the terminal methyl group in the case of the cis-isomers of 3,4-epoxypentan-1-ol and 4,5-epoxyhexan-1-ol than in the case of the trans-isomers, Fig. 22.



trans-



cis-

FIG 22

Such a difference in steric hindrance may have considerable effect on the products and product ratios obtained from the different epoxide isomers. From the carbon chain lengths chosen a study can be made of which ring size will form preferentially when there is a choice between two, i.e. four and five, five and six, and six and seven membered rings. Finally, if there is any change of mechanism of the reaction when the hydroxyl group is readily available to attack the epoxide function, and when it is not, then evidence for this may show up in the products formed.

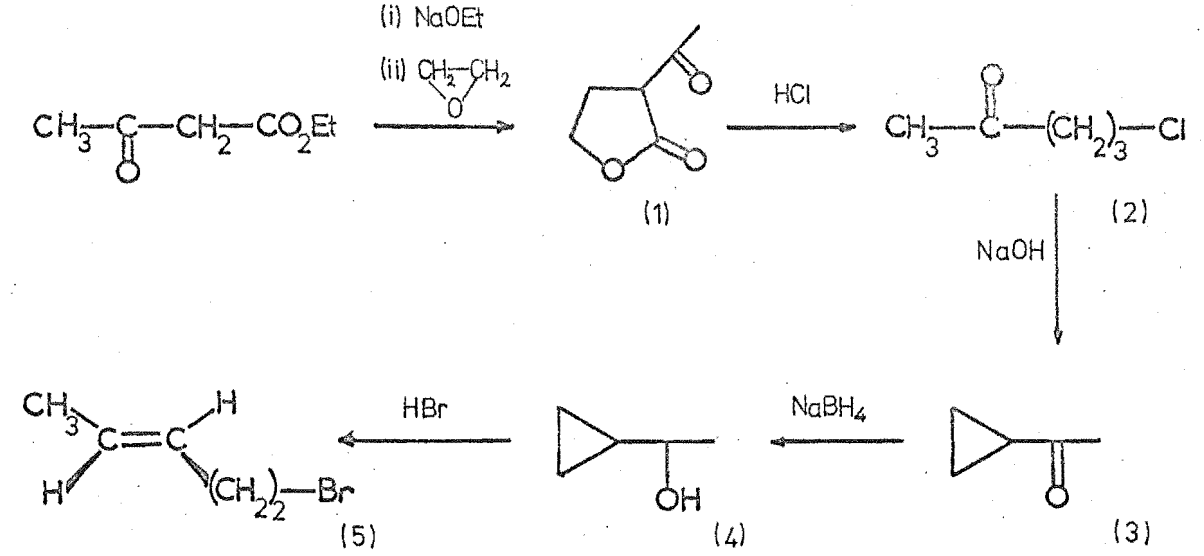
All the above effects will have an influence on the type of product formed and its yield. Where the influence of each effect can be separated a considerable amount of data should be available for each one.

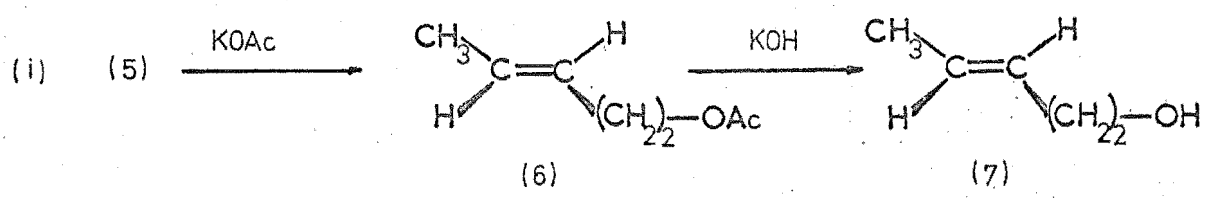
THE ACID CATALYSED REARRANGEMENTS OF EPOXIDES WITH NEIGHBOURING HYDROXYL GROUPS

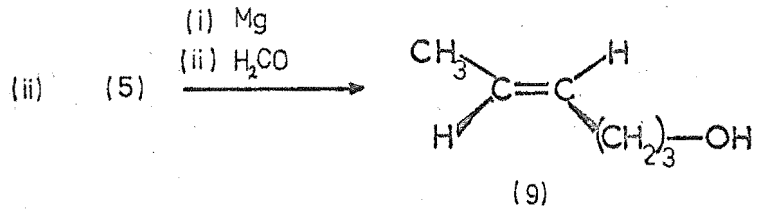
Preparation of the Epoxyalcohols

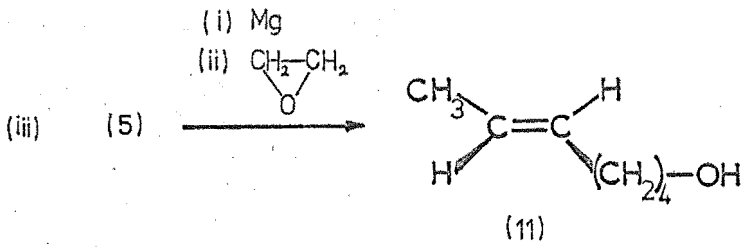
After an extensive literature search the synthetic routes to the required alkenes outlined in Fig. 23 were selected. It may be seen from the diagram that trans-1-bromopent-3-ene (5) was used as a common intermediate for the syntheses of the three trans-alkene alcohols (7,9,11). The cis-alkene alcohols (16,18,20) were then prepared from the corresponding trans-isomers by the pathway shown in Fig. 23 (iv). The first three reactions of the synthetic pathway to trans-1-bromopent-3-ene were all reasonably straightforward and involved:- the reaction of the sodium salt of ethyl acetoacetic ester with ethylene oxide to form 3-acetyldihydrofuran-2(3H)-one (1), the conversion of (1) to 5-chloropentan-2-one (2) and the elimination of the elements of hydrochloric acid from (2) to give cyclopropylmethyl ketone (3). However, the α-methylcyclopropanemethanol (4) formed on reduction of ketone (3) by sodium borohydride in methanol could only be isolated from basic solution, since in the presence of acid, alcohol (4) reacted rapidly with the methanol to form the methyl ether.

Julia et al.[40] rearranged alcohol (4) with hydrobromic acid and on the basis of infra-red evidence claimed that the product was trans-1-bromopent-3-ene (5). In this work it was found (g.l.c.) that the reaction yielded a 1:9 mixture of cis- to trans-1-bromopent-3-enes from which pure material could not be separated by a distillation.


(i) NaOEt
(ii) CH2—CH2 / O
HCl
(1)
(2)
NaOH
(3)
NaBH4
(4)
HBr
(5)


(i)
(5)
KOAc
KOH
(6)
(7)


(ii)
(5)
(i) Mg
(ii) H2CO
(9)


(iii)
(5)
(i) Mg
(ii) CH2—CH2 / O
(11)

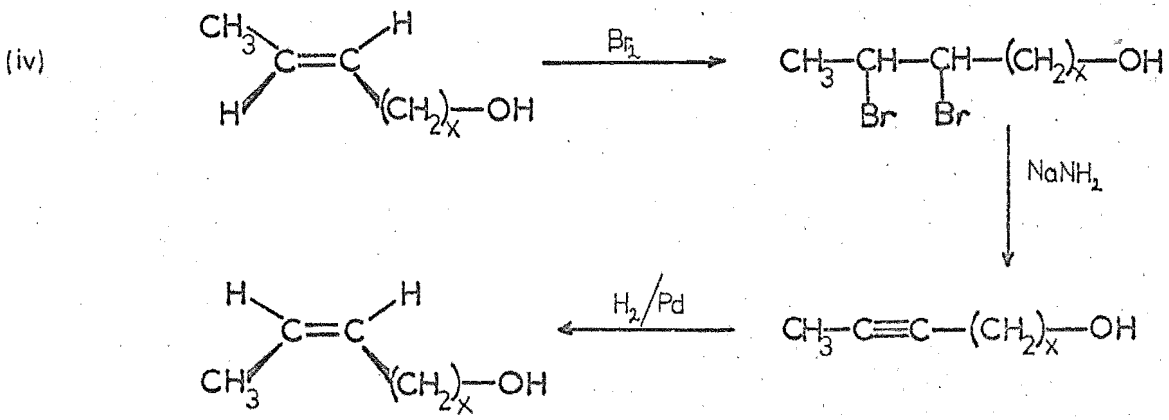

(iv)
Br2
NaNH2
H2/Pd

FIG 23

Preparation of epoxypentanols (22,28)

For the efficient displacement of the bromine atom of (5) by acetate ion (Fig. 23(i)) the reaction conditions had to be such that the attacking species were better nucleophiles than the carbon-carbon double bonds. If this were not the case the carbon-carbon double bond would participate in the reaction and a cyclopropane ring would be formed, Fig. 24.

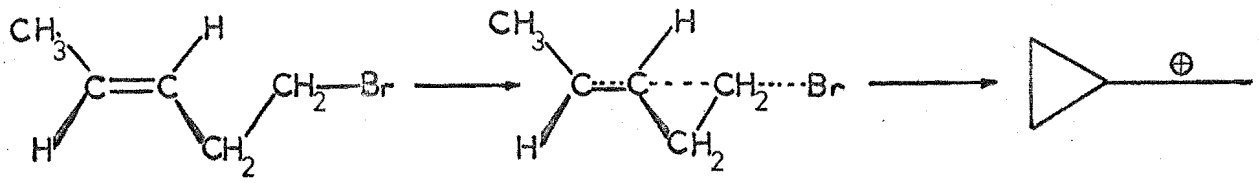


FIG 24

Consequently, when the bromoalkene (5) was reacted with an excess of silver acetate α-methylcyclopropanemethanol acetate was the only major product, but when potassium acetate in glacial acetic acid was used a 70% yield of the required pent-3-en-1-ol acetates was obtained. This mixture of the cis- and trans-pent-3-en-1-ol acetates (15,6) was inseparable by g.l.c., but the alcohols (16,7) obtained by alkaline hydrolysis of the mixture were separable by either g.l.c. or distillation.

trans-3,4-Epoxypentan-1-ol (22) was made by oxidation of the appropriate alkene by an ethereal solution of monoperoxyphthalic acid. Although the epoxide (22) tended to decompose on some g.l.c. columns it appeared to be stable when FFAP was used as a liquid phase.

The conversion of trans-pent-3-en-1-ol (7) into pent-3-yn-1-ol (12) by bromination and then subsequent dehydrobromination with sodamide (Fig. 23(iv)) was attempted a number

of times but in no run was the yield greater than 13%. Initially it was thought that the low yield was due to the conversion of the dibromoalcohol into 3-bromo-2-methyltetrahydrofuran (69) by the intramolecular displacement of a bromide ion by the hydroxyl group before the required dehydrobromination with the sodamide could occur. In order to prevent this presumed cyclization reaction the alcohol (7) was converted into acetate (6) before bromination. This procedure failed to raise the yield of the required alkyne (12); the hydroxyl group was then protected as the tetrahydropyranyl derivative but to no avail, the yield of acetylene (12) remained low. Different rates of addition of the dibromo compound to the sodamide, which was always present in large excess, and very careful isolation of the products also failed to raise the yield of the acetylene (12). Finally the low efficiency of the conversion of the dibromoalcohol into the acetylene (12) was accepted and the crude product subjected to a careful distillation using a twentyfour inch annular teflon spinning band column. Due to the similarity between the boiling points of the acetylene (12) and the impurities only a small fraction of pure compound could be obtained. The other fractions were subsequently purified by preparative g.l.c.

Hydrogenation of the acetylene (12) was carried out over the Lindlar catalyst[37]. The reduction of the acetylene (12) required a reaction time of two weeks in spite of the replacement of the catalyst on two occasions in that period. Even after two weeks the hydrogenation was not complete and the cis-pent-3-en-1-ol (16) was purified by preparative g.l.c. before being converted into the required epoxide (28).

Preparation of Epoxyhexanols (24,30)

Initially a (1:9) mixture of cis- and trans-hex-4-en-1-ols (18,9) was synthesized by the addition of formaldehyde to the Grignard reagent made from the mixed bromoalkenes (5), Fig. 23(ii). However, this reaction was rather inefficient and in addition the mixture of alcohols (18,9) obtained could not be resolved by g.l.c. It was therefore decided to make the trans-hex-4-en-1-ol (9) by the reaction pathway shown in Fig. 25 as this was reported[42] to give only the trans alkene (9) in good yield. No difficulties were encountered in any of the three reactions involved in the pathway.

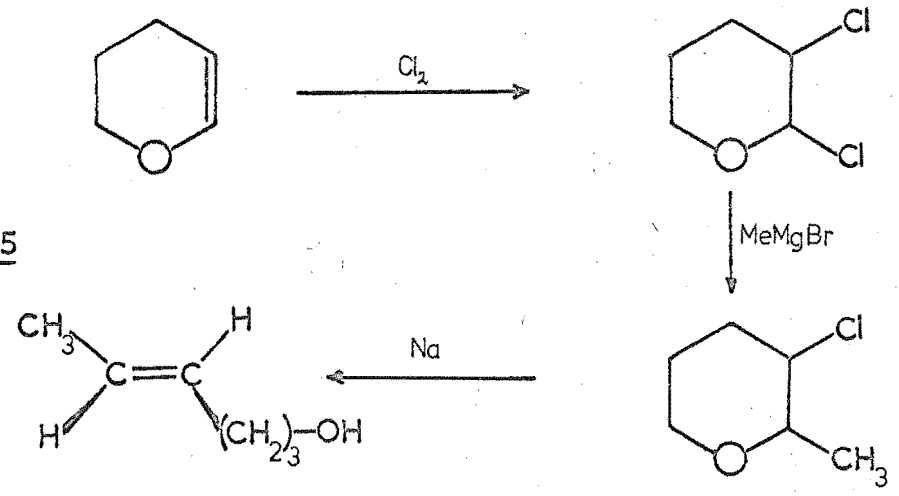


FIG 25

When the samples of trans-hex-4-en-1-ol (9) obtained by the two different methods outlined above were reacted with an ethereal solution of monoperoxyphthalic acid, different product ratios were found, although in each case no 4,5-epoxy-hexan-1-ol (30 or 24) was obtained. The products formed by the oxidation of the mixed hex-4-en-1-ols (18,9) synthesized by the first method (Fig. 23(ii)) were erythro-2-(1-hydroxyethyl)-tetrahydrofuran (36, 76%), trans-2-methyltetrahydropyran-3-ol (40, 14%) and threo-2-(1-hydroxyethyl)tetrahydrofuran (38, 10%). In the case of the trans-hex-4-en-1-ol (9) made by the second method (Fig. 25) only 5% of threo-2-(1-hydroxyethyl)tetrahydro-

furan (38) was formed while both other products (36,40) remained proportionally the same. From the information above it appears that due to the participation of the hydroxyl group, even a weak acid such as phthalic acid can catalyse the isomerization of the epoxides (30,24) as they are formed, Fig. 26.

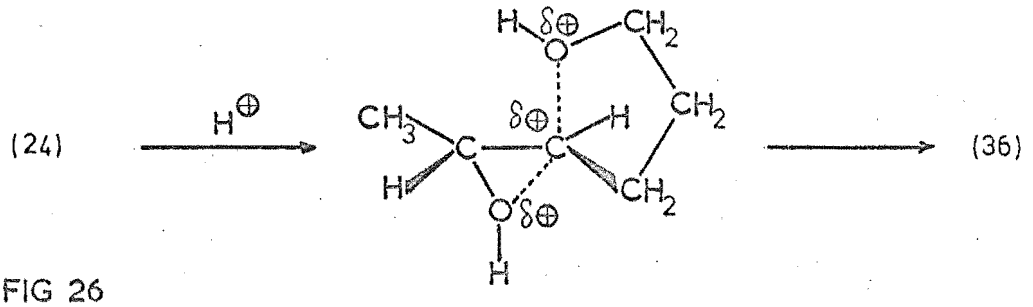


FIG 26

It also seems likely from the product ratios that erythro-2-(1-hydroxyethyl)tetrahydrofuran (36) and trans-2-methyltetrahydropyran-3-ol (40) came from the trans-4,5-epoxyhexan-1-ol while the threo-isomer (38) came from the cis-4,5-epoxyhexan-1-ol. This means that the trans-alkene (9) made by the second method (Fig. 25) probably contained 5% of the cis- isomer (18).

In order to obtain completely pure trans-hex-4-en-1-ol (9) hex-4-yn-1-ol (13) was reduced by sodium in liquid ammonia. The acetylene (13) was obtained by bromination and dehydrobromination of the mixed alkenes (18,9) in a similar fashion to the synthesis of pent-3-yn-1-ol (12). However, in this case the reaction was much cleaner and gave a higher yield of the acetylene (13), which was relatively easy to purify by a spinning band distillation. Oxidation of the pure trans-alkene (9) by monoperoxyphthalic acid in ether gave only erythro-2-(1-hydroxyethyl)tetrahydrofuran (36, 84%) and trans-2-methyltetrahydropyran-3-ol (40, 16%).

In an effort to obtain trans-4,5-epoxyhexan-1-ol (24) an alkaline epoxidation[50] of the alkene (9) was attempted.

Although the presence of epoxide protons in the crude reaction mixture was revealed by the n.m.r. spectrum, the material rearranged to the cyclic ethers (36,40) during distillation and attempted analysis by g.l.c.; this method was abandoned. As a last resort the trans-hex-4-en-1-ol acetate (8) was made and this was epoxidized by monoperoxyphthalic acid. The trans-4,5-epoxyhexan-1-ol acetate (25) was stable to both distillation and g.l.c. and was readily separable from the cis-isomer (31) by both methods. Attempts were made to remove the acetate group from the epoxide (25) by hydrolysis with sodium hydroxide in methanol but this gave the isomerised compounds erythro-2-(1-hydroxyethyl)tetrahydrofuran (36, 96%) and trans-2-methyltetrahydropyran-3-ol (40, 4%). Hydrolysis of the epoxyacetate (25) with sodium hydroxide in aqueous methanol at -20°C followed by careful isolation and a molecular distillation finally gave trans-4,5-epoxyhexan-1-ol shown to be pure by its n.m.r. and i.r. spectra.

The different ratios of erythro-2-(1-hydroxyethyl)tetrahydrofuran (36) to trans-2-methyltetrahydropyran-3-ol (40) obtained when trans-epoxyhexanol (24) was subjected to acid and base catalysed isomerization is thought to be due to the differing inductive effects of the alcohol function as compared to the alkoxide ion. In the acid catalysed rearrangement the attacking nucleophile is the alcohol group whereas in the base catalysed reaction this role is assumed by the alkoxide ion. In the transition states of both types of isomerization a slight positive charge resides on the epoxide carbon being attacked by the nucleophile, Fig. 5[65]. The inductive effect of an alkoxide ion would be expected to help stabilize this charge while the inductive effect of an alcohol group would

tend to destabilize it. Hence under acid catalysed conditions the inductive effect would favour the six-membered ring while under base catalysed conditions the five-membered ring would be favoured.

The hydrogenation of hex-4-yn-1-ol (13) over Lindlar catalyst gave an almost quantitative yield of cis-alkene (18). This alkene was subsequently converted into the cis-epoxy-acetate (31) and then hydrolysed to cis-4,5-epoxyhexan-1-ol in a similar manner to the trans-isomer (9). The pure cis-epoxyalcohol (32) obtained after a molecular distillation was as unstable as the highly reactive trans-epoxyalcohol (24).

Preparation of Epoxyheptanols (26,32)

A 1:9 mixture of cis- to trans-hept-5-en-1-ol (20,11) was prepared by adding ethylene oxide to the Grignard reagent made from 1-bromopent-3-ene (5). The reaction was carried out according to the method of Dreger[43] and presented no difficulties except that the cis- and trans-isomers (20,11) could not be separated by g.l.c. When the mixture of alkenes (20,11) was reacted with monoperoxyphthalic acid in ether the epoxides (32,26) were formed but could not be purified as they isomerised to erythro- and threo-2-(1-hydroxyethyl)tetrahydropyran (34,35) during distillation and on g.l.c. Consequently the trans-5,6-epoxyheptan-1-ol acetate was synthesized, purified and hydrolysed to trans-5,6-epoxyheptan-1-ol in a similar manner to its C_6-analogue.

The conversion of the mixed alkenes (20,11) to cis-hept-5-en-1-ol by bromination, dehydrobromination and then hydrogenation over Lindlar catalyst followed a similar pattern to the reaction sequence of the hexenols (18,9). The cis-alkene (20) was acetylated, epoxidized, purified and

hydrolysed to give cis-5,6-epoxyhexan-1-ol (30).

The Acid Catalysed Reactions of the Epoxyalcohols

The acid catalysed reactions of the epoxyalcohols (22,24, 26,28,30,32) were all carried out at room temperature in dilute solution. Ether was the solvent of choice although, in the case of the epoxypentanols (22,28), benzene and dichloromethane were also used. The high dilution of the epoxide in the solvent (1 mg/ml) was used in order to minimize the amount of polymerization[57] and thereby encourage cyclization reactions (Fig. 26) or rearrangements to carbonyl compounds, Fig. 1(b).

The reactions of all the epoxyalcohols in ether were catalysed by an excess of BF_3-etherate (2.5 M), toluene-p-sulphonic acid, or trifluoroacetic acid at the same concentration as the Lewis acid. In the case of the reactions of the epoxypentanols (22,28) in benzene and in dichloromethane BF_3-etherate, at a concentration of one seventh of that of the epoxide, was the only acid used.

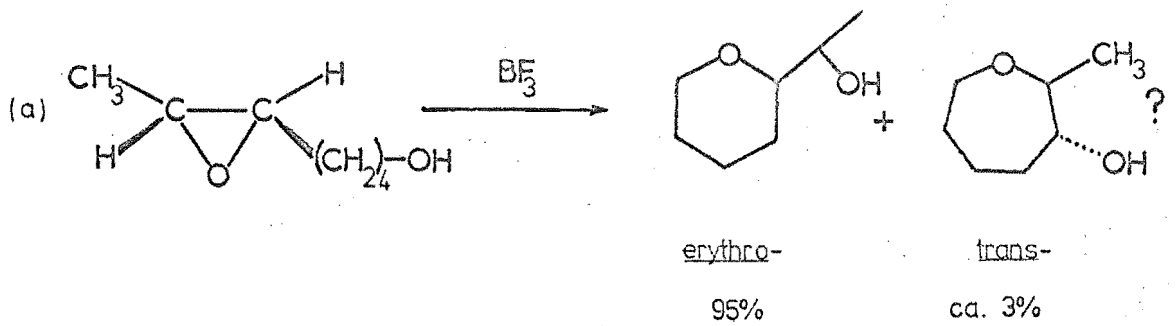
The absolute yields of the products from the acid catalysed reactions of all the epoxyalcohols were calculated by g.l.c. using mesitylene (1,3,5-trimethylbenzene) and cyclohexanol as internal standards. These internal standards were added to the reaction mixture after the acid had been neutralized and thus circumvented possible problems from their involvement, even only as a solvent effect, in the rearrangement process. The solvent was then removed by a careful distillation such that none of the cyclic reaction products or internal standards were removed. The conditions for the removal of the solvent from the products of the acid catalysed reactions of the epoxides were checked by running a blank on

each. These blanks contained known amounts of the appropriate cyclic product and internal standard in the same concentration as in the actual reaction mixtures and were worked up in a similar fashion. In no case was the ratio of the product to internal standard measurably affected by the removal of the solvent.

The internal standards were calibrated against the major reaction product in each case and isomers with the same molecular formula were assumed to have the same response factor. Absolute yields of the reaction products were estimated to be accurate to within ±5% although the error for unidentified compounds may well have been much greater since their response factors remain unknown. The products obtained from the acid catalysed reactions were identified by their n.m.r. and i.r. spectra after they had been purified by preparative g.l.c. and if the compound was not reported in the literature an elemental analysis or accurate mass measurement of the parent ion was obtained. Any reaction products that were identified by g.l.c. retention times alone were compared with an authentic sample on three separate columns employing different liquid phases.

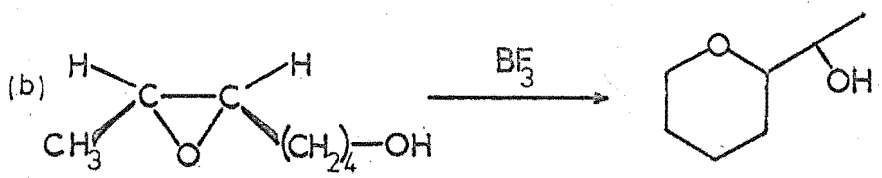
Rearrangements of Epoxyheptanols (26,32) and Epoxyhexanols (24,30)

Dilute solutions of the cis- and trans-isomers of 5,6-epoxyheptan-1-ol (32,26) and 4,5-epoxyhexan-1-ol (30,24) were isomerised, using BF_3-etherate as a catalyst, to tetrahydropyran (34,35,40) and tetrahydrofuran (36,38) derivatives in high yield, Fig. 27. The stereochemistry of these tetrahydropyran and tetrahydrofuran products showed that in all cases

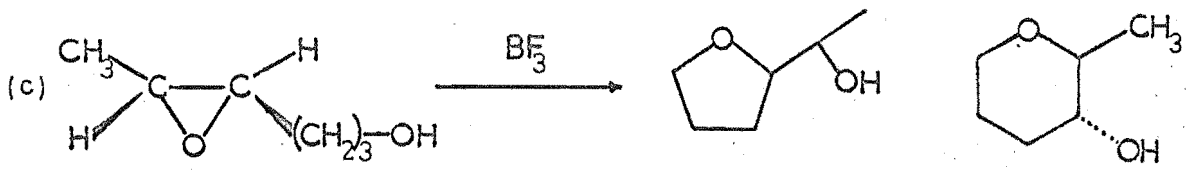


erythro-
95%

trans-
ca. 3%

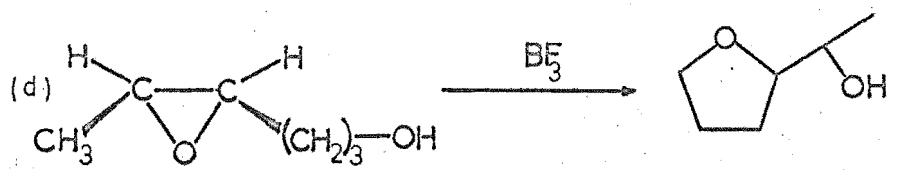


threo-
98%



erythro-
84%

trans-
16%



threo-
98%

FIG 27

the epoxide ring opened with inversion of configuration.

cis-5,6-Epoxyheptan-1-ol (32) was isomerised by the Lewis acid to threo-2-(1-hydroxyethyl)tetrahydropyran (98%, 35) while the trans-isomer (26) gave erythro-2-(1-hydroxyethyl)-tetrahydropyran (95%, 34) and an unidentified compound which was thought to be trans-2-methyloxepan-3-ol (ca. 3%, 70). The sole product of the acid catalysed rearrangement of cis-4,5-epoxyhexan-1-ol (30) was threo-2-(1-hydroxyethyl)tetrahydropyran (98%, 35) whereas the trans-epoxide (24) gave erythro-2-(1-hydroxyethyl)tetrahydrofuran (84%, 34) and trans-2-methyltetrahydropyran-3-ol (16%, 40).

The threo- and erythro-isomers of 2-(1-hydroxyethyl)tetrahydrofuran (38,36) and 2-(1-hydroxyethyl)tetrahydropyran (35, 34) were differentiated by comparison of their dilute solution i.r. spectra[44]. All four of the compounds are capable of forming intramolecular hydrogen bonds between the cyclic ether oxygen and the hydroxyl group. When they are intramolecularly hydrogen bonded, the hydroxy ethers exist in conformations in which methyl-hydrogen eclipsing occurs in the threo-isomers (35,38) and methyl-methylene eclipsing occurs in the erythro-isomers (34,36), Fig. 28. As a result of these steric interactions intramolecular hydrogen bonding is much less favoured in the erythro-compared to the threo-isomers.

FIG 28

Hence in a dilute solution intramolecular hydrogen bonding is

complete in the threo-isomers whereas in the erythro-isomers a significant proportion of the molecules have, at any one time, free hydroxyl groups. The solution i.r. spectra of the latter compounds therefore exhibit absorptions due to both free and intramolecularly bonded hydroxyl groups while the spectra of the former compounds show only the hydrogen bonded absorption.

The erythro-compounds might be expected to be more polar than the threo-isomers and this was apparent in their behaviour on g.l.c. On polar columns the erythro-isomers always had greater retention times than the corresponding threo-isomers.

The stereochemistry of the trans-2-methyltetrahydropyran-3-ol (40) was elucidated by preparing the acetoxy derivative (41) (so that the proton on C3 could be differentiated from those on C2 and C6) and observing the n.m.r. coupling constants of the hydrogen atoms on C2 and C3. The coupling of 11 Hz suggested that the two protons were trans-diaxial and hence the hydroxyl and the methyl groups were trans-diequatorial.

Mechanism of Rearrangements of Epoxyheptanols (26,32) and Epoxyhexanols (24,30)

The mechanism by which the acid catalysed reactions of both geometric isomers of 5,6-epoxyheptan-1-ol (26,32) and 4,5-epoxyhexan-1-ol (24,30) proceeds is reflected in the facility with which the reactions occur and the structure of the products. The fact that the only products formed were those which arose by inversion of configuration at an epoxide carbon atom indicates that the reaction mechanism is A2 or borderline A2 [7,16], i.e. there is considerable participation by the

hydroxyl group in the ring opening of the epoxide, Fig. 26. If the reactions proceed *via* a carbonium ion intermediate partial or complete racemization would be expected in the products formed. This racemization is due to the ability of a discrete carbonium ion to rotate and thus lose its original stereochemical identity, Fig. 12.

Additional evidence for an A2 mechanism comes from the ease of reaction of the epoxyalcohols. All the epoxides and especially the 4,5-epoxyhexanols are sensitive to isomerization under mildly acidic conditions compared with normal secondary epoxides and thus assistance from the hydroxyl group in ring opening is indicated. When the Dreiding models of the epoxides (26,32,24,30) were constructed it was found that in the two *trans*-isomers (26,24) the alcohol function could readily approach the rear of either of the two epoxide ring carbon atoms. In the *cis*-isomers (32,30) steric repulsion from the terminal methyl group would hinder hydroxyl group approach to C6 in epoxide (32) and C5 in epoxide (30) but no such effect protected the epoxide carbons nearest the hydroxyl functions, Fig. 22. Thus in all four epoxyalcohols the hydroxyl groups have easy access to the rear of at least one of the epoxide carbons and the compounds are ideally arranged for isomerization *via* an A2 mechanism.

A further indication of the mechanism of isomerization of the epoxyalcohols (24,26,30,32) can be obtained from a consideration of the products formed. Regardless of the mechanism by which the reaction takes place there is a choice of two ring sizes for the products formed. With epoxides (26,32) a six- or seven-membered ring product may be formed, whereas with epoxides (24,30) there is a choice between a five-

and a six-membered product. If the isomerizations proceed *via* discrete carbonium ions the epoxide ring would tend to open such that the positive charge resides on the carbon atom furthest away from the hydroxyl group with its destabilizing inductive effect[36]. This means that products with the greater ring size would be expected to predominate.

In the absence of steric effects isomerizations that proceed by an A2 mechanism should, if a choice is available between a five- and a six-membered ring, or a six- and a seven-membered ring, give products with the smaller ring size as these are the easier to form[61]. The experimental results for the reactions of the *trans*-isomers (24,26), where the hydroxyl group has free access to both epoxide carbons, follow just such a trend, Fig. 27. For the *cis*-isomers (30,32) the tendency to form products with the lower ring size is strongly reinforced by one of the epoxide carbons being rendered inaccessible to the hydroxyl group by the steric hindrance of the terminal methyl group, Fig. 22.

Consideration of all the experimental data from the acid catalysed isomerizations of the epoxyalcohols shows conclusively that the reactions proceed *via* an A2 or borderline A2 mechanism.

Rearrangements of Epoxypentanols (22,28)

Isomerization of *trans*-3,4-epoxypentan-1-ol (22) was effected by BF_3-etherate under the same conditions as for the epoxyheptanols (26,32) and epoxyhexanols (24,30) and a good yield of 2-methyltetrahydrofuran-3-ols (42,45) was obtained (Fig. 29(a)). Unlike the previous examples this rearrangement gave a product, *cis*-2-methyltetrahydrofuran-3-ol (8%, 45) which involved retention of configuration of the epoxide ring

carbon atoms. Two unidentified products that were considered to be fluorohydrins by their g.l.c. behaviour were also detected but they were not present in sufficient concentration for isolation attempts to be successful.

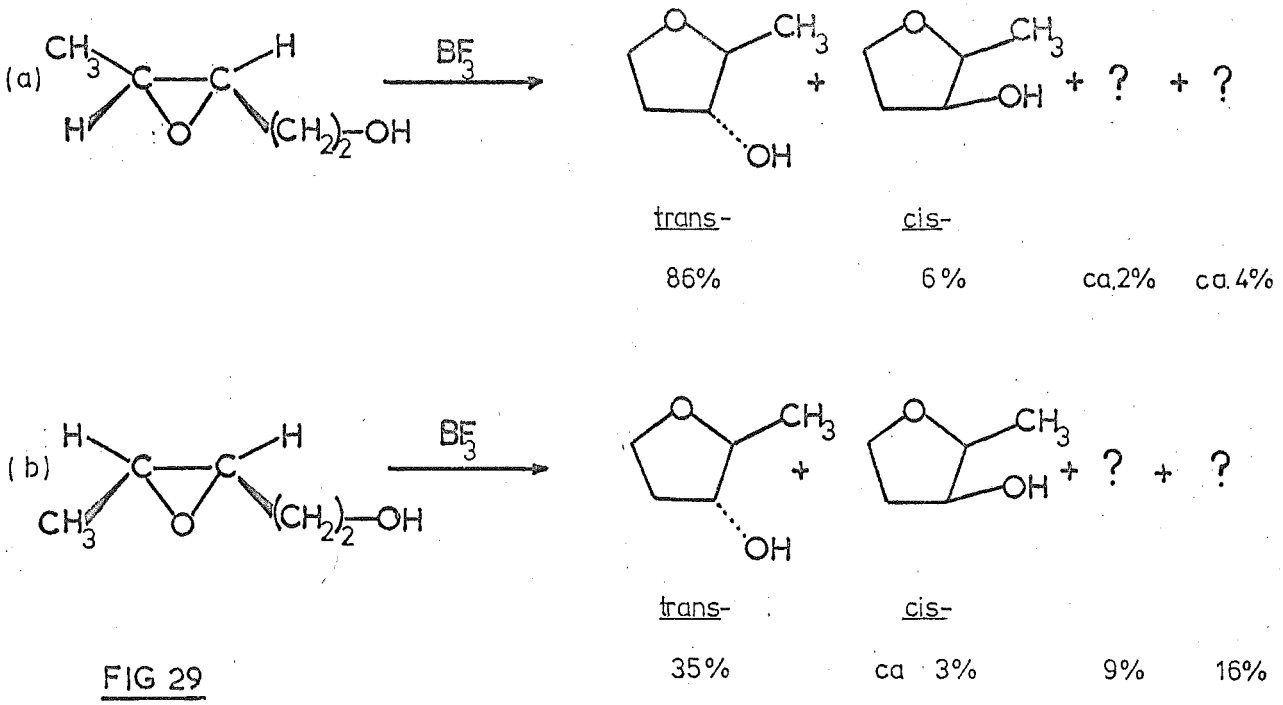


FIG 29

Reaction of a dilute solution of cis-3,4-epoxypentan-1-ol (28) in ether by BF_3-etherate gave radically different products (Fig. 29(b)) to those produced in the previous isomerizations. In this case the yield of tetrahydrofuran derivatives (42,45) was lower and the major product trans-2-methyltetrahydrofuran-3-ol (42) was formed with inversion of configuration. The two unidentified products were considered to be fluorohydrins by their g.l.c. behaviour.

The stereochemistry for each of the cis- and trans-2-methyltetrahydrofurans (42,45) was assigned by comparison (g.l.c.) with the products of reduction of the corresponding ketone (44). Dihydro-2-methylfuran-3(2H)-one (44) was prepared by oxidizing a mixture of 2-methyltetrahydrofuranols with Jones reagent and then reducing the purified ketone by sodium in moist ether. As this type of reduction is under thermo-

dynamic control the most stable product will be present in the greatest yield. By analogy with the reduction of 1-methylcyclopentan-2-one by a similar method[49], it was expected in this case that the most stable product would be the trans-alcohol (42) as there is less steric interaction between the methyl and hydroxyl groups than in the cis-alcohol (45). A g.l.c. trace of the reduction mixture of ketone (44) showed only two products. The one with the longer retention time being present in 88% yield and the other in 12% yield. On this evidence the trans-configuration was assigned to the alcohol with the greatest g.l.c. retention time.

Mechanism of Rearrangements of Epoxypentanols (22,28)

The ratio (10:1) of trans-2-methyltetrahydrofuran-3-ol (45) to the cis-isomer (42) formed in the isomerization of both the epoxypentanols (22,28) is close to the composition of the mixture produced on equilibration of the epimeric alcohols. Consequently the possibility of product equilibration under the reaction conditions had to be eliminated. Reduction of dihydro-2-methylfuran-3(2H)-one (44) with $LiAlH_4$ in ether gave a 45:55 mixture of the cis- and trans-alcohols (45,42). These alcohols were subsequently purified by preparative g.l.c. and then subjected to the epoxide rearrangement conditions. In no case could epimerization of an alcohol be detected.

The possibility that the product of retention of configuration arose via a fluorohydrin intermediate by a double inversion process (Fig. 30) was rendered improbable when the epoxyalcohols (22,28) were reacted with trifluoroacetic acid and toluene-p-sulphonic acid.

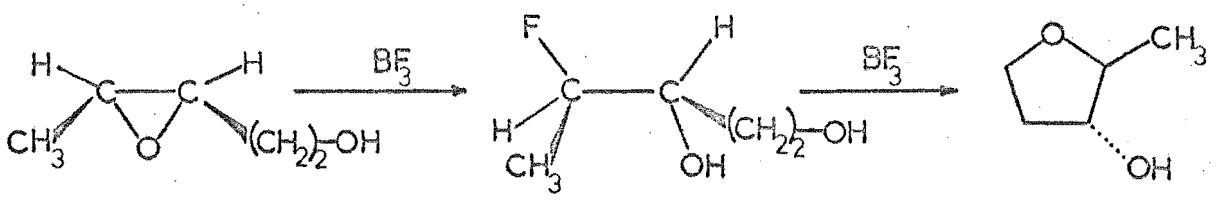


FIG 30

Isomerizations catalysed by these acids gave very similar product ratios to those obtained with BF_3-etherate except for the reaction of trans-3,4-epoxypentan-1-ol with toluene-p-sulphonic acid. In all the reactions some compound with retention of configuration was detected among the products; for the reaction of the trans-epoxide (22) with toluene-p-sulphonic acid the ratio of cis- to trans-alcohols (45,42) was 55:45. Although it is still possible that products formed with retention of configuration during the isomerizations of the epoxypentanols by the toluene-p-sulphonic acid and trifluoroacetic acid involved a double inversion mechanism, proceeding via a toslylate and trifluoroacetoxy intermediate respectively, it is unlikely[63].

It appears therefore that the reactions of the epoxypentanols (22,28), unlike the previous ones (24,26,30,32) do not proceed by an A2 or a borderline A2 mechanism. This change in mechanism is most probably a response to the decreased ability of the hydroxyl group to participate in the reactions. Whereas in the isomerizations of the epoxyalcohols (24,26,30,32) the hydroxyl function has free access to the rear of at least one of the epoxide ring carbon atoms this is not the case for the epoxypentanols (22,28). In the latter compounds the carbon chain containing the nucleophile is too short to allow hydroxyl participation during the opening of the epoxide ring.

It is possible that the product with retention of configuration from trans-3,4-epoxypentan-1-ol (22) could arise by syn-displacement of the epoxide oxygen atom by the hydroxyl group (Fig. 31) but it is very improbable that this sterically unfavourable mechanism would give such a high yield of this type of product from the cis-isomer (28).

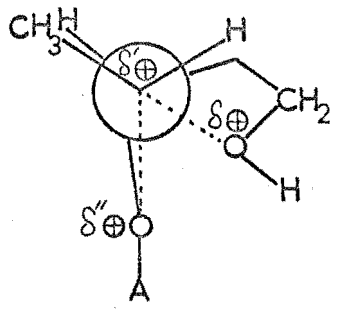


FIG 31

The product compositions from the BF_3-etherate catalysed reactions of cis- and trans-epoxypentanol can, however, be rationalized in terms of a comparatively long lived secondary carbonium ion intermediate. If the lifetime of such a carbonium ion is much greater than the time taken for conformational change then the same equilibrium ratios of rotamers (Fig. 32), and hence the same product ratios, will be formed from both epoxides (28,22). However, such a mechanism does not explain the large difference in product yields from the two isomers (28,22) and it also seems unlikely that the secondary carbonium ion would have such a long lifetime.

The product compositions from the BF_3-etherate catalysed reactions of cis- and trans-epoxypentanol (28,22) can also be rationalized in terms of a short lived secondary carbonium ion intermediate as long as three assumptions are made.

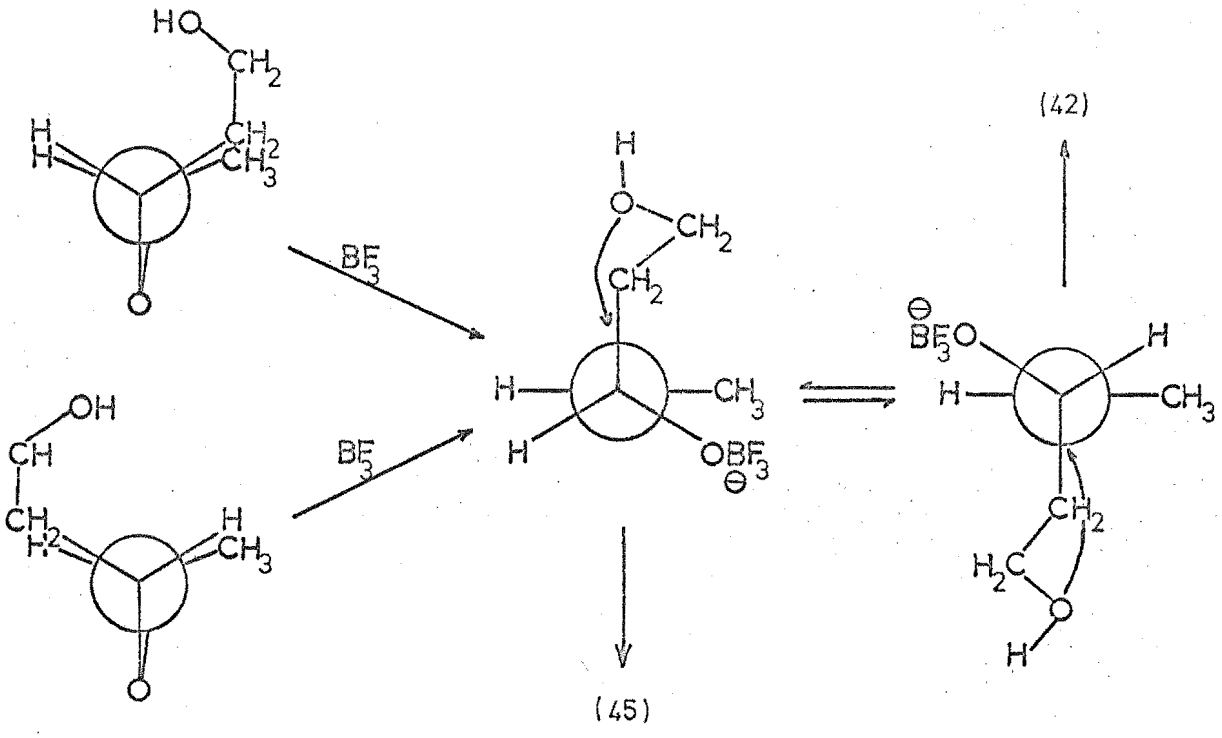


FIG 32

The first two assumptions are the same as those needed to explain the product compositions obtained from cis- and trans-epoxybutane (page 22) while the third one is: methyl-methylene torsional strain is less than that between a methyl group and a boron trifluoride coordinated oxygen atom.

On reacting the epoxypentanols (22,28) with BF_3-etherate the epoxide ring should cleave such that the positive charge resides on the carbon atom furthest from the hydroxyl group[36]. The conformations initially adopted by the carbonium ions are represented in Figs 33,34. Study of these diagrams reveals that in the conformations where hydride shift is possible it is discouraged by: (a) the increasing torsional strain between two reasonably large groups that such a shift would bring about, (b) the inductive effect of the hydroxyl group, (c) nucleophilic competition from the hydroxyl function.

After trans-3,4-epoxypentan-1-ol has reacted with BF_3-etherate to form a carbonium ion on C4 the C3 atom may rotate in a clockwise or anticlockwise direction, Fig. 33(i) and (ii).

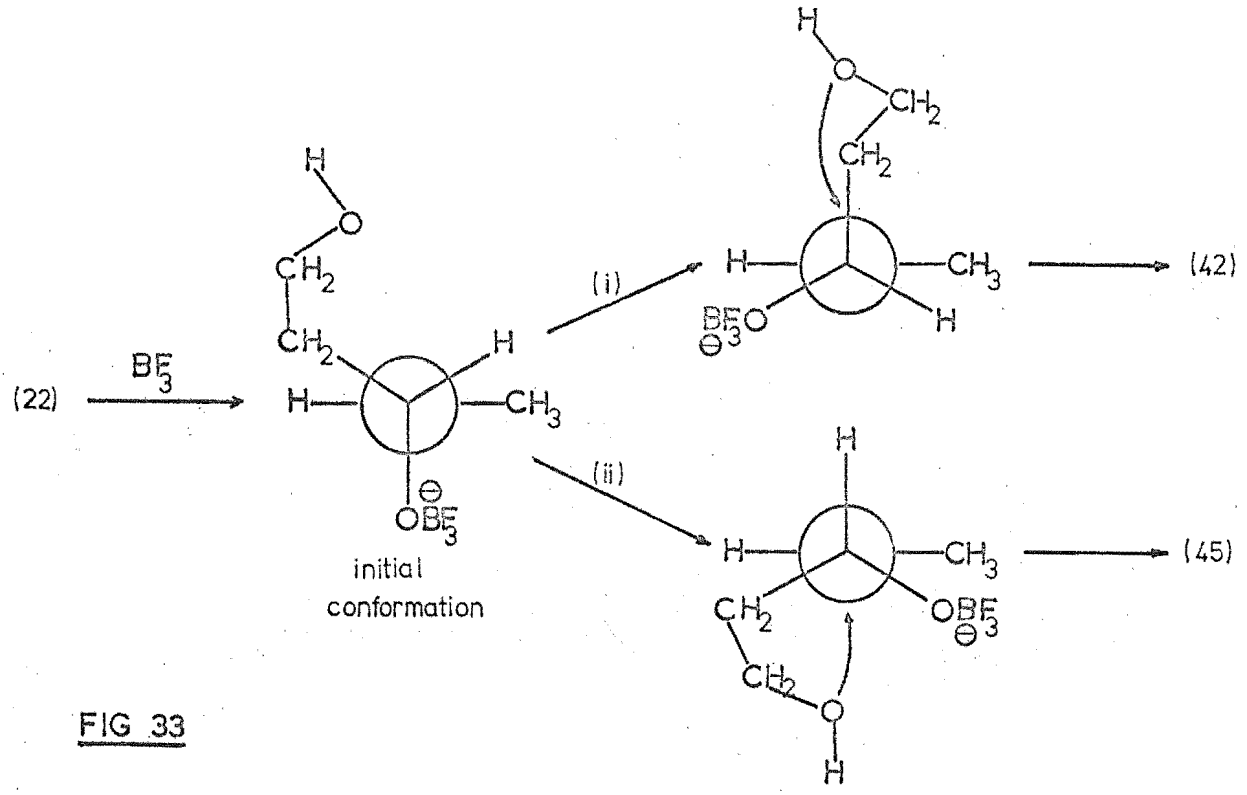


FIG 33

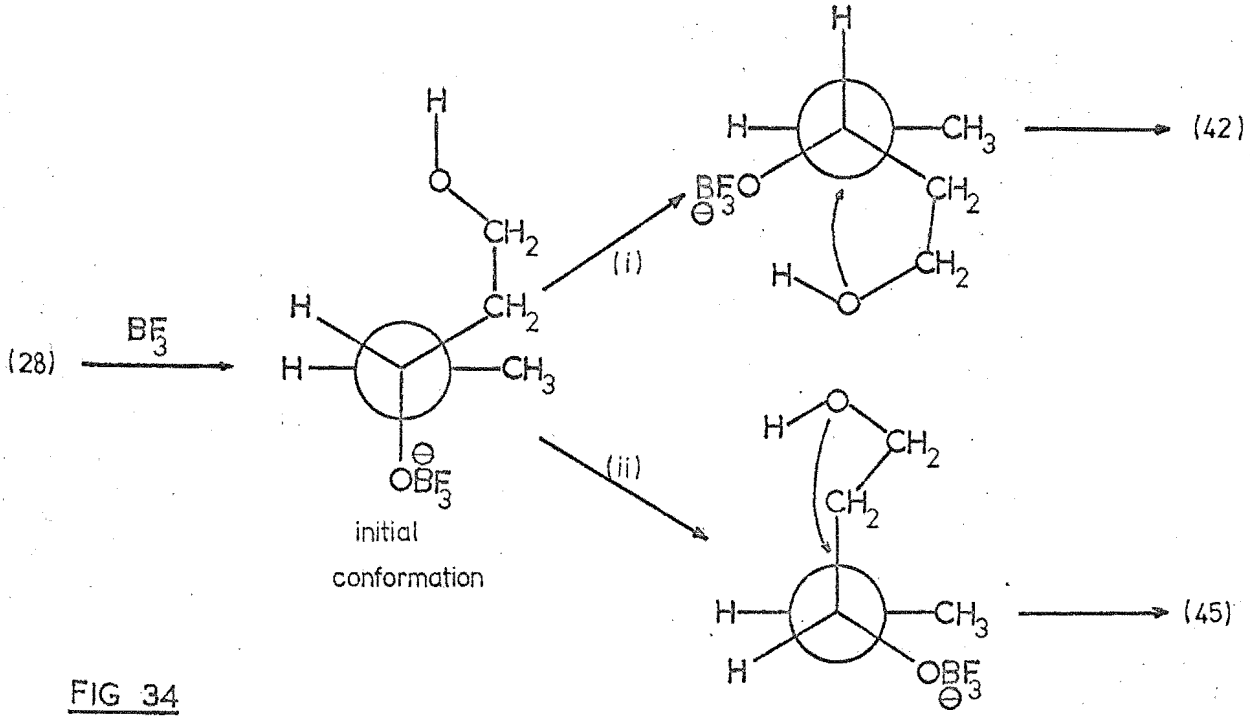


FIG 34

Clearly rotation in a clockwise direction (i) will be favoured as this relieves the torsional strain between the methyl group and the Lewis acid coordinated oxygen atom. Movement in this direction also places the hydroxyl group in an increasingly favourable position to attack the carbonium ion to give trans-2-methyltetrahydrofuran-3-ol (42) as the only

product. The optimum conformation for such nucleophilic attack being reached when the C2 atom eclipses the vacant p orbital, Fig. 33(b). Rotation of the C3 atom in an anticlockwise direction (ii) will be much less favourable due to the increasing torsional interaction between the methyl group and the Lewis acid coordinated oxygen. However much of this strain will be relieved as the hydroxyl group attacks the carbonium ion and sp^3 hybridization is regained at this carbon atom. Consequently cis-2-methyltetrahydrofuran-3-ol (45) should also form.

The formation of a carbonium ion at C4 upon cleavage of the epoxide ring in cis-4,5-epoxypentan-1-ol (28) by BF_3-etherate is represented diagrammatically in Fig. 34. Unlike the intermediate formed from the trans-epoxide (22) in this case it is not immediately obvious whether rotation by C3 is more favourable in a clockwise or anticlockwise direction. Although rotation in an anticlockwise direction (ii) strongly favours nucleophilic attack of the carbonium ion by the hydroxyl group such movement also rapidly increases the torsional strain between the methyl group and the Lewis acid coordinated oxygen, (c).

If rotation of C3 occurs in a clockwise direction (i) methyl-methylene eclipsing must be overcome. However, once this is achieved (b) the hydroxyl group can then easily attack the carbonium ion to form trans-2-methyltetrahydrofuran-2-ol (42) as no serious torsional interactions are involved.

From the argument presented above it is clear that if a short lived carbonium ion intermediate is used to rationalize the products obtained from the isomerization of cis-3,4-epoxypentan-1-ol (28) rotation of C3 in a clockwise direction

must be favoured. The most likely explanation for this bias is that methyl-Lewis acid coordinated oxygen eclipsing must be energetically less favourable than methyl-methylene eclipsing.

Only two thirds of the initial amount of cis-3,4-epoxypentan-1-ol (28) isomerised by BF_3-etherate in ether was accounted for by tetrahydrofuranol derivatives (42,45) and "fluorohydrins"*, the remainder of the products were not detectable by g.l.c. It seems probable that the low recovery of products was due to the intervention of fragmentation reactions, the lower molecular weight products of which may have been lost during the isolation process; however, losses through polymerization could not be completely discounted. Although the energy of methyl-methylene eclipsing may be less than that for methyl-Lewis acid coordinated oxygen eclipsing it is still considerable (the highest energy barrier to rotation in butane is approximately 5 k cal.mole^{-1})[64]. In the carbonium ion formed from the cis-epoxypentanol (28) such an energy barrier must be overcome before nucleophilic attack can occur but this is not the case for the cation formed from trans-epoxypentanol (22). Thus if competing processes such as fragmentation reactions can take place they would be more likely to occur during reaction of the cis-(28) rather than the trans-epoxide (22).

The two possible fragmentation reactions for cis-3,4-epoxypentan-1-ol (28) are represented in Fig. 35. The first process which gives the enol forms of propanal and acetaldehyde appears more likely to occur than the second one which gives

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* The "fluorohydrins" are probably formed by nucleophilic attack with inversion in the usual way as the retention times of the two isomers formed in this reaction are similar, but different, to those formed from trans-3,4-epoxypentan-1-ol (22).

but-1-en-3-ol and formaldehyde. However, propanal and acetaldehyde are both volatile and tended to decompose during analysis making unambiguous identification impossible. None of the unsaturated alcohol (72) could be detected in any of the reactions.

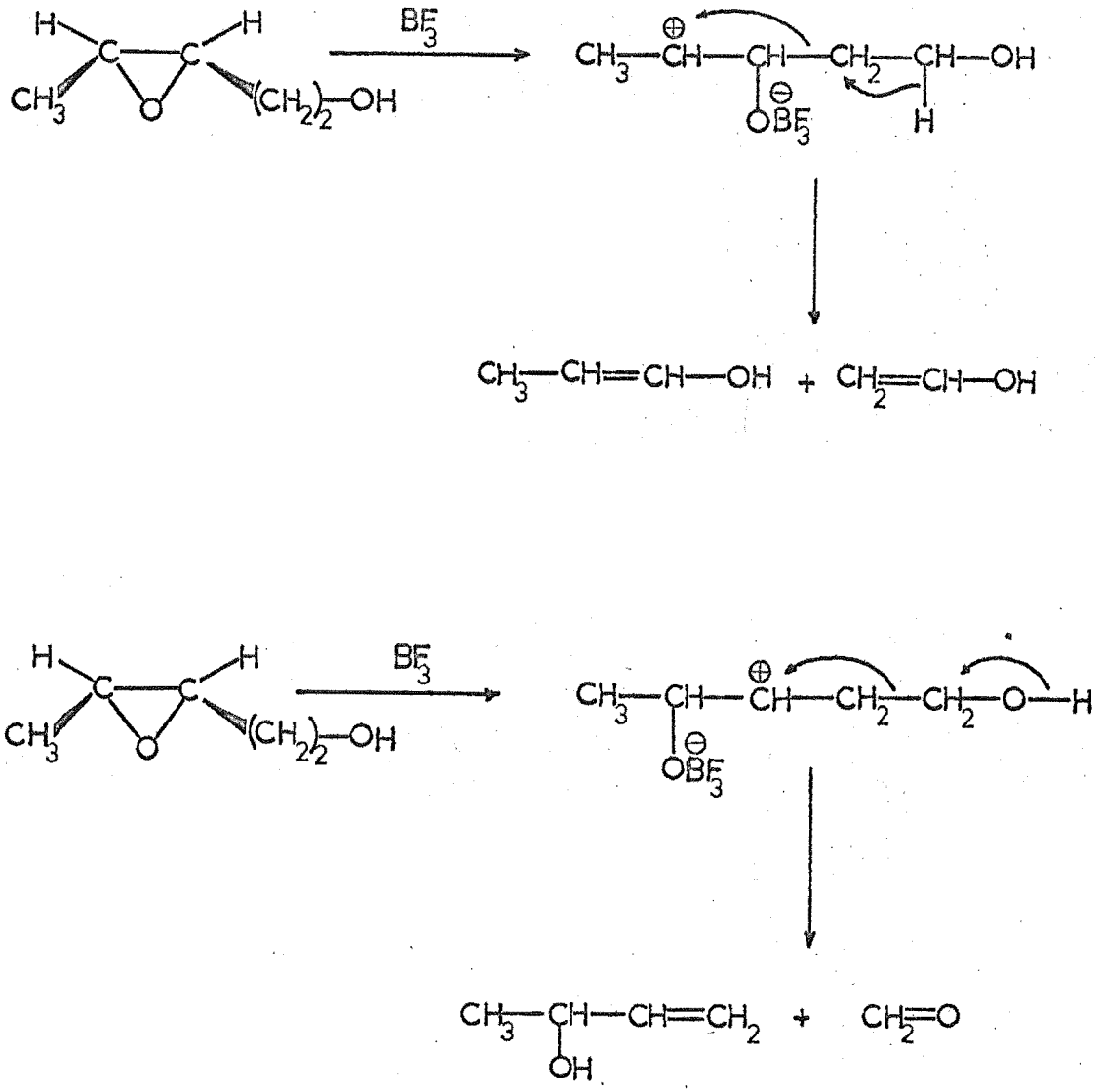


FIG 35

As the products formed by the isomerizations of cis- and trans-3,4-epoxypentan-1-ols in ether by BF_3-etherate can best be explained in terms of a carbonium ion intermediate the epoxides (22,28) were reacted with the same Lewis acid in two different solvents in order to study the effect on the product ratios. In both benzene and dichloromethane the ratios of

tetrahydrofuranol products (42,45) from the trans-epoxide were similar to those obtained for ether solutions. The overall yields however were much lower being only 30% when the solvent was benzene and even less (20%) when dichloromethane was used.

The reaction of cis-3,4-epoxypentan-1-ol (28) in benzene or dichloromethane with BF_3-etherate yielded only a trace of trans-2-methyltetrahydrofuran-3-ol (42) but no other products were detected by g.l.c.

The lower yields of tetrahydrofuranol products (42,45) from the Lewis acid catalysed reactions of the epoxypentanols (22,28) in non-participating solvents were probably due to two factors. The first of these is the instability of the secondary carbonium ion when formed in such solvents and hence the greater likelihood of fragmentation reactions. The second is that the Lewis acid coordinated epoxide may be insoluble in the solvents giving a separate phase where the high concentration of substrate leads to linear polymerization as a significant reaction. These polymers would be non-volatile and hence would not be detected by g.l.c.

THE ACID CATALYSED REARRANGEMENTS OF EPOXIDES WITH NEIGHBOURING ACETATE GROUPS

Introduction

During the study of the rearrangement of the epoxypentanols (22,28) attempts were made to prepare the diastereoisomers of 4-fluoro-3-hydroxypentan-1-ol (73) and 3-fluoro-4-hydroxypentan-1-ol (74) in sufficient yield so that they could be isolated and their structures confirmed. In addition it was intended that these fluorohydrins (73,74), possible intermediates in the rearrangement of epoxides (28,22), would be subjected to the epoxide rearrangement conditions.

Attempted synthesis of the fluorohydrins (73,74) by reaction of the trans-3,4-epoxypentan-1-ol (22) with anhydrous hydrofluoric acid or anhydrous fluoroboric acid in ether resulted in the production of tetrahydrofuranol derivatives (42,45) in high yield. In order to prevent this participation of the hydroxyl group in the reaction the acetoxy derivative of trans-pent-3-en-1-ol was prepared and the corresponding epoxide (23) made by oxidation with monoperoxyphthalic acid. When an approximately 0.5 M ether solution of the crude epoxy-acetate (23) was reacted with anhydrous fluoroboric acid a thick white precipitate formed immediately. Over a period of about thirty minutes this precipitate changed to a viscous liquid that remained largely insoluble in ether. On the addition of anhydrous potassium carbonate the unidentified liquid gradually redissolved in the solvent. A subsequent g.l.c. trace of the reaction mixture showed it to consist largely of one compound with a shorter retention time than the starting material. The compound was purified by preparative

g.l.c. The n.m.r. and i.r. spectra and elemental analysis for this compound indicated that it was either the cis- or the trans-2-methyltetrahydrofuran-3-ol acetate (46 or 43). In order to establish unequivocally the stereochemistry the acetoxy derivatives of authentic cis- and trans-2-methyltetrahydrofuran-3-ols (45,42) were prepared. The product obtained from the isomerization of trans-3,4-epoxypentan-1-ol acetate (23) was identical in all respects to cis-2-methyltetrahydrofuran-3-ol acetate (46).

Mechanisms of the Acid Catalysed Reactions of Epoxides with Neighbouring Acetate Groups

(i) Reactions of alicyclic epoxides with neighbouring ester groups

Previous work on the rearrangement of epoxides with neighbouring ester groups has been confined mainly to alicyclic compounds. If the stereochemistry is favourable, participation by the ester carbonyl function may occur during the acid catalysed opening of the epoxide ring. Such participation by neighbouring ester carbonyl groups acting as nucleophiles is very similar to that observed in certain substitution reactions of tosylates, halides and similar derivatives. These reactions have been extensively investigated by Winstein et al.[59] and Buchanan et al.[66].

The most favourable stereochemistry for neighbouring group participation by an ester carbonyl group at a centre of developing positive charge in a cyclic system is shown in Fig. 36. Reactions of type (a) involve attack of an axial ester group on the carbon atom bearing an equatorial leaving group, the substituents being in a trans-1,3 relationship. The resulting acetonium ion is greatly stabilized by

mesomerism[67]. The other type of acetonium ion (b) which can form without appreciable bond angle strain is one using cis-bonds on adjacent carbon atoms (a 1,2 acetonium ion).

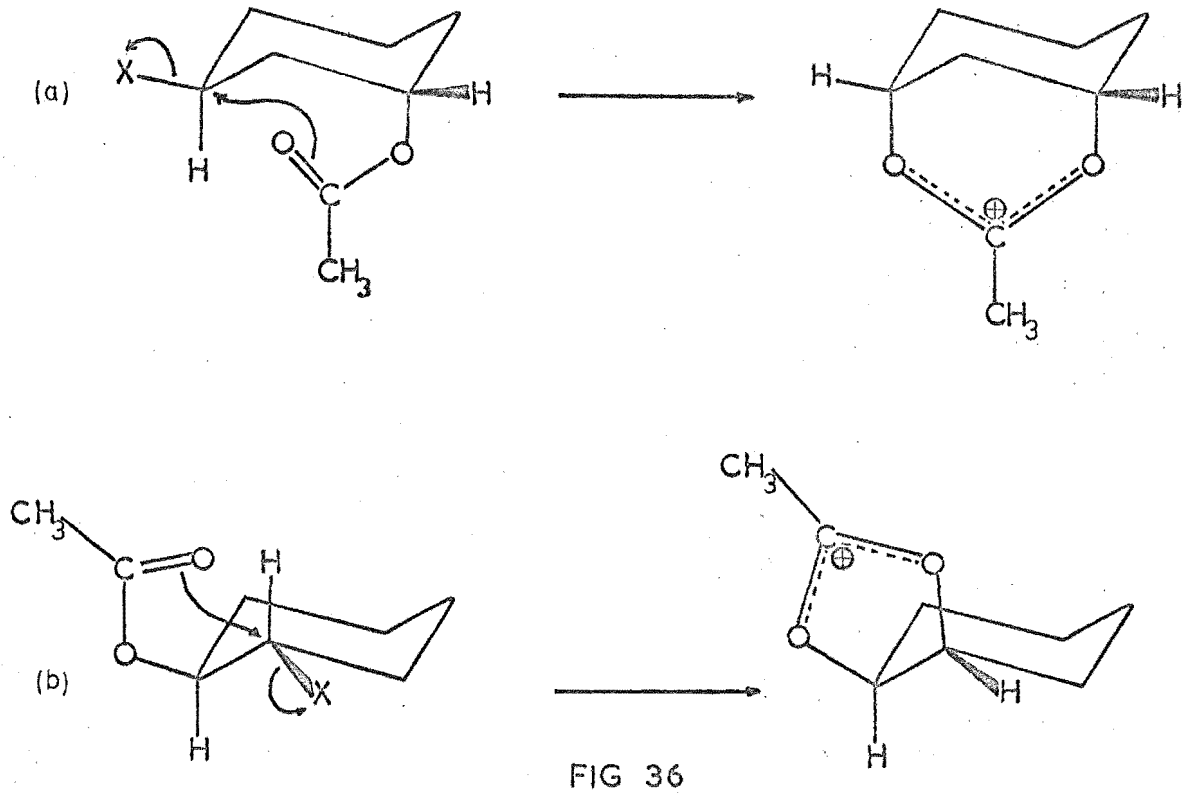


FIG 36

Substitution processes leading to either a 1,2 or a 1,3-acetonium ion can be considered as an internal A2 substitution proceeding with inversion of configuration at the reaction centre. Where the groups concerned have the right steric relationship such reactions proceed with great facility and generally in preference to attack by an external nucleophile. The subsequent fate of the acetonium ion depends on the molecular environment and reaction conditions.

An example of ester carbonyl participation during acid catalysed opening of an epoxide ring is the reaction of 3β,17β-diacetoxy-4α,5α-epoxyandrostane to give 4β,17β-diacetoxy-androstane-3β,5α-diol, Fig. 37. On the other hand some epoxides derived from enol acetates give products that cannot be explained simply by nucleophilic attack by an ester carbonyl group and

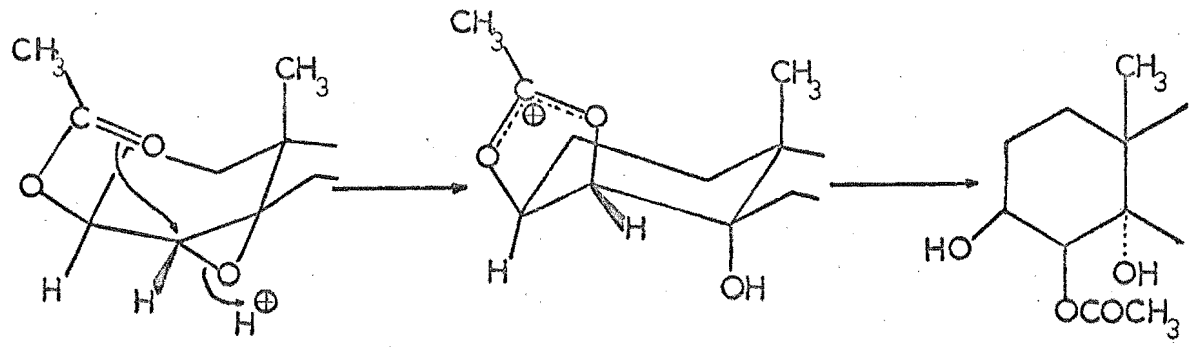


FIG 37

these reactions may proceed by an alternative mechanism[68], Fig. 38.

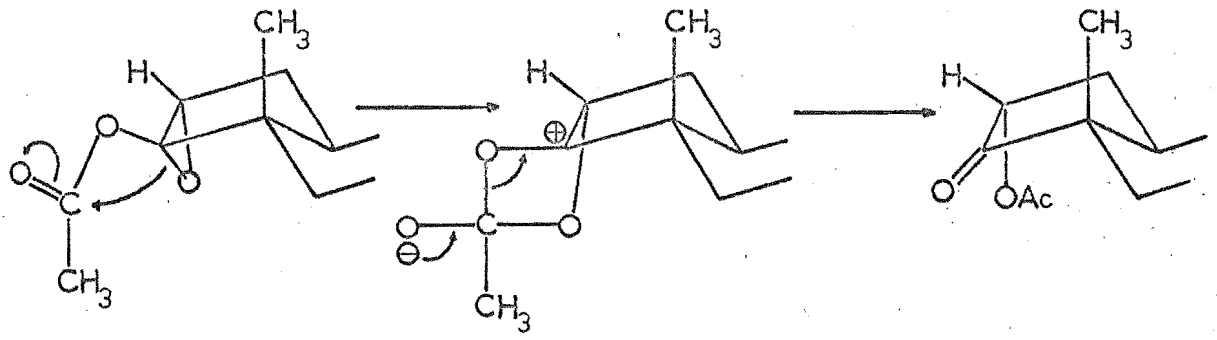
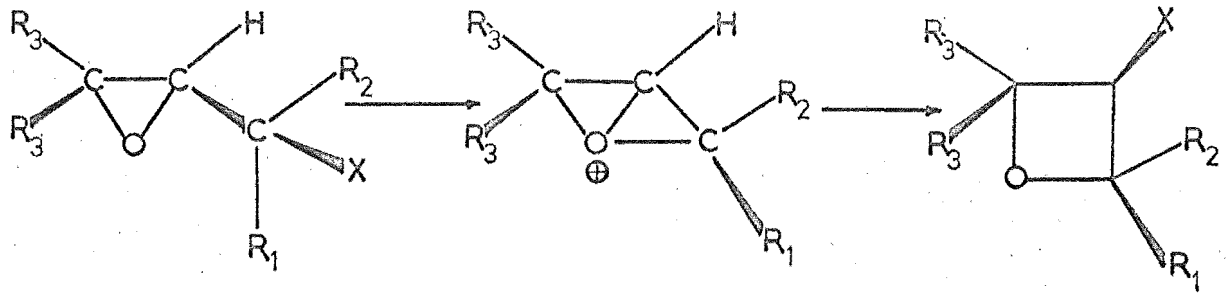


FIG 38

(ii) Reactions of acyclic epoxides with neighbouring ester groups

Two papers on the isomerization of acyclic epoxides containing neighbouring ester groups have been published[11,69] and both of these have reported unusual products compared to those obtained from the cyclic epoxides. Richey and Kinsman[69] have isomerised the esters of several 2,3-epoxypropan-1-ols to esters of oxetan-3-ols during solvolysis reactions, Fig. 39. Although these workers were unable to elucidate the stereochemistry of the oxetan-3-ol ester products they proposed a mechanism for their formation. In their opinion the reaction mechanism involved an oxabicyclobutonium ion (Fig. 39(b)) formed by neighbouring group displacement of the ester function by the epoxide oxygen.



R_1, R_2, R_3 = alkyl or hydride group

X = ester group

FIG 39

This intermediate could then be subject to nucleophilic attack by the acid anion to give the oxetan-3-ol ester products.

Such a mechanism seems very unlikely if only because of the considerable steric strain that must be involved in an oxabicyclobutonium ion intermediate.

Thomas and Pawlak[11] have rearranged 2,5,5-trimethyl-3,4-epoxyhept-6-en-2-ol acetate with Dowex 50 in ether and obtained an oxetan-3-ol acetate in high yield, Fig. 40. These

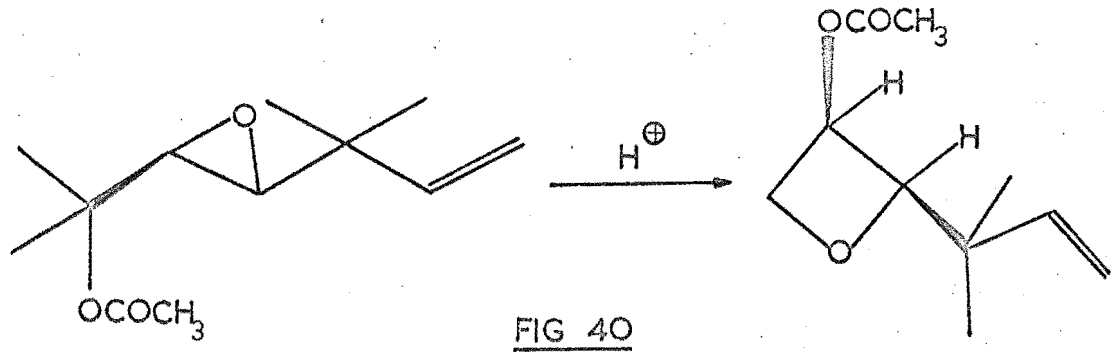


FIG 40

workers also could not obtain incontrovertible evidence for the stereochemistry of the oxetan-3-ol acetate but strongly suspect that the cis-isomer is formed. In order to explain the major product obtained from this reaction, an ortho ester was postulated as an intermediate. However, Thomas and Pawlak considered it it be unlikely that initial acid catalysed nucleophilic attack of the epoxide by the ester

carbonyl group occurred to form an acetonium ion followed by further reaction with the remaining hydroxyl group, to give an ortho ester (Fig. 41).

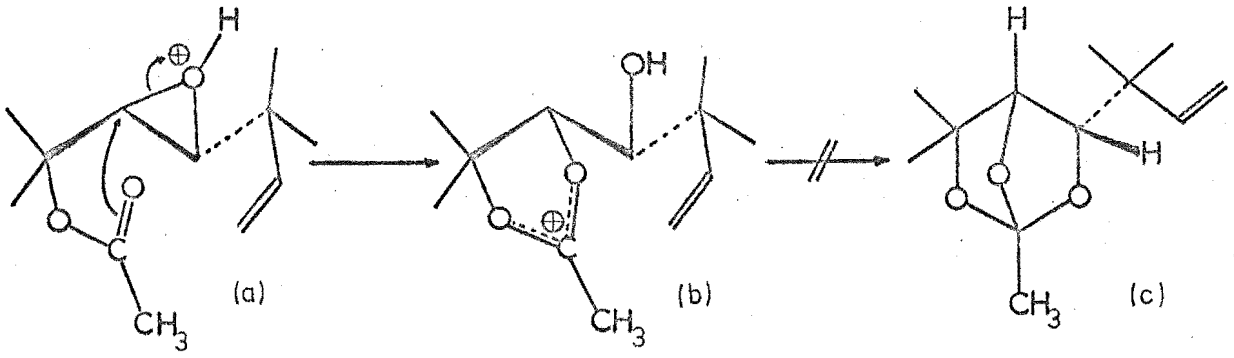


FIG 41

This opinion was based on the fact that such an intermediate would involve serious steric clashing of the methyl and dimethylallyl groups in endo-positions on either side of the trioxanorbornane ring (c). These workers postulate that the more stable exo-isomer (Fig. 42(d)) is the actual ortho ester intermediate and that once this is formed it decomposes to give the oxetan-3-ol acetate[70]. The mode of formation of the exo-substituted ortho ester has not been demonstrated but a pathway involving a tertiary epoxide intermediate has been proposed (Fig. 42(c)).

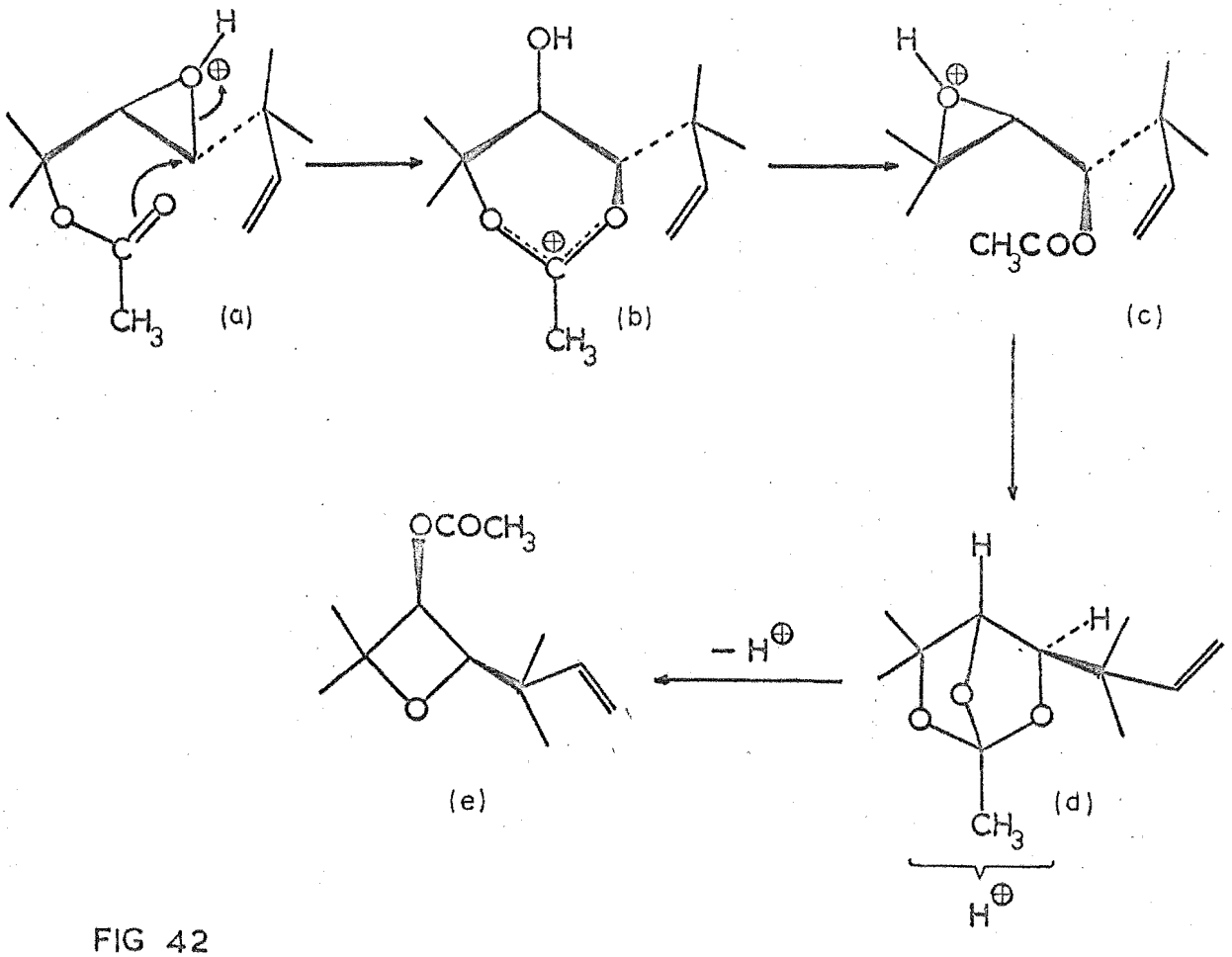


FIG 42

The Acid Catalysed Reactions of Epoxyacetates (23,29,25,31,27,33)

In order to study more fully the mechanism by which the isomerizations of acyclic epoxides with neighbouring ester groups proceed the pure cis- and trans- isomers of 3,4-epoxy-pentan-1-ol acetate (23,29), 4,5-epoxyhexan-1-ol acetate (25,31) and 5,6-epoxyheptan-1-ol acetate (27,33) were prepared. These compounds were then reacted with BF_3 etherate in ether after which the products were analysed by g.l.c.

Although the cis- and trans-epoxyheptanol acetates (27,33) and cis- and trans-epoxyhexanol acetates (25,31) are stable to g.l.c. considerable care is needed when attempting to analyse or purify the epoxy acetates (23,29) by this method. It was found that if the injector part or column were not both meticulously cleaned before use the epoxides isomerised readily to methyltetrahydrofuranol acetates (43,46). The liquid

phase least likely to have an adverse effect on these compounds was found to be FFAP.

Rearrangements of Epoxypentanol Acetates (23,29)

Reaction of a 0.5 M solution of pure trans-3,4-epoxypentan-1-ol acetate (23) in ether with BF_3-etherate gave similar products and yields to those obtained with anhydrous fluoroboric acid. Upon addition of the Lewis acid coarse white crystals were rapidly precipitated but these soon began to dissolve to give a liquid that was insoluble in ether. After addition of aqueous potassium carbonate this viscous liquid redissolved in the solvent. The reaction was found (g.l.c.) to have yielded cis-2-methyltetrahydrofuran-3-ol acetate (64%, 46) and traces of three other compounds with retention similar but not identical to authentic 5-acetoxypentan-2-one (73).

In an attempt to stop the separation of the crystalline material, and thus possibly increase the yield of products, the isomerization was carried out at high dilution in ether. Even at these low concentrations however, a faint cloudiness could be detected in the reaction mixture unless the Lewis acid was added over a period of about two hours; the yield of product (46) was only slightly raised to 68%.

Reactions of dilute ether solutions of cis-3,4-epoxypentan-1-ol acetate (29) with BF_3-etherate under similar conditions to those used for the isomerization of the trans-isomer (23) gave 40% yields of the major product, trans-2-methyltetrahydrofuran-3-ol acetate (43). Traces of two products with retention times similar to authentic 5-acetoxypentan-2-one (73) were detected but no other products.

Rearrangements of Epoxyhexanol Acetates (25,31)

Although the reactions of trans-4,5-epoxyhexan-1-ol acetate (25) with BF_3-etherate were carried out in ether at a similar dilution (1 mg/ml) to that used for the epoxypentanol acetates (23,29) more than twice as much Lewis acid and considerably longer times were needed for complete reaction. The products and their absolute yields obtained from the reaction were: threo-2-(1-acetoxyethyl)tetrahydrofuran (62%, 39), 6-acetoxyhexan-3-one, (ca. 3%, 48), 6-acetoxyhexan-2-one (trace, 50), erythro-4-hydroxy-5-fluorohexan-1-ol acetate (17%, 61) and erythro-5-hydroxy-4-fluorohexan-1-ol acetate (13%, 64).

The reactions of cis-4,5-epoxyhexan-1-ol acetate (31) with BF_3-etherate under similar conditions to those used for the trans-isomer (25) yielded: erythro-2-(1-acetoxyethyl)-tetrahydrofuran (30%, 37), 6-acetoxyhexan-3-one (30%, 48), 6-acetoxyhexan-2-one (14%, 50), threo-4-hydroxy-5-fluorohexan-1-ol acetate (14%, 54) and threo-5-hydroxy-4-fluorohexan-1-ol acetate (7%, 58).

Products formed by the Lewis acid catalysed reactions of both epoxide isomers (25,31) can be classified into three groups: (i) isomerizations involving neighbouring group participation by the acetate function to give 2-(1-acetoxyethyl)-tetrahydrofuran products (37,39) with retention of configuration, (ii) isomerizations involving simple rearrangement, without participation of the acetate function to give carbonyl compounds (48,50), and (iii) the reaction of the epoxide with a fluorine containing nucleophile to give fluorohydrin products (54,58,61,64) with inversion of configuration. Products belonging to one class of compounds have quite

different g.l.c. retention times to those belonging to another class. The 2-(1-acetoxyethyl)tetrahydrofurans (37,39) have somewhat shorter, while the carbonyl products (48,50) have longer, retention times than the starting epoxides (24,31). Fluorohydrin products (54,58,61,64) all have much greater retention times than any of the other compounds.

It was possible to purify all the compounds in the first two classes by preparative g.l.c. and so their structures could be assigned unambiguously from a consideration of their n.m.r. and i.r. spectra. However, in order to differentiate between threo- and erythro-2-(1-acetoxyethyl)tetrahydrofuran (39,37) it was necessary to convert the compounds into the known alcohols (38,36).

Attempts to purify the fluorohydrins (54,58,61,64) by preparative g.l.c. failed due to decomposition of the compounds during the process. As these products could not be obtained pure their g.l.c. response factors could not be compared with the other compounds. However, response factors for fluorohydrins and carbonyl compounds formed from trans-epoxyheptanol acetate (27) were comparable (see page 65).

In order to increase the stability of the fluorine containing compounds towards purification by preparative g.l.c. they were converted into the corresponding fluorodiacetates (55,59,62,65) and these products were readily isolated. Elemental analyses showed that all four compounds had the same ratios of elements while n.m.r. and i.r. evidence enabled assignment of the fluorine and acetoxy groups to specific carbon atoms. However, insufficient data was available to differentiate between the possible diastereoisomers. Proof of the stereochemistry of the threo- and erythro-fluorohydrins

(54,58; 61,64) was eventually obtained by reaction of the fluorodiacetates (55,59; 62,65) with potassium tert.-butoxide in tert.-butanol. Under these conditions both the fluorodiacetates derived from the cis-epoxyacetate (31) gave threo-2-(1-hydroxyethyl)tetrahydrofuran (38) as the sole product. This product (38) was also the only one obtained when the cis-epoxyacetate was reacted with potassium tert. butoxide. The only way in which a 4-acetoxy-5-fluorohexan-1-ol acetate (55 or 62) can form such a product (38) is for the cis-epoxide intermediate (Fig. 43) to be formed.

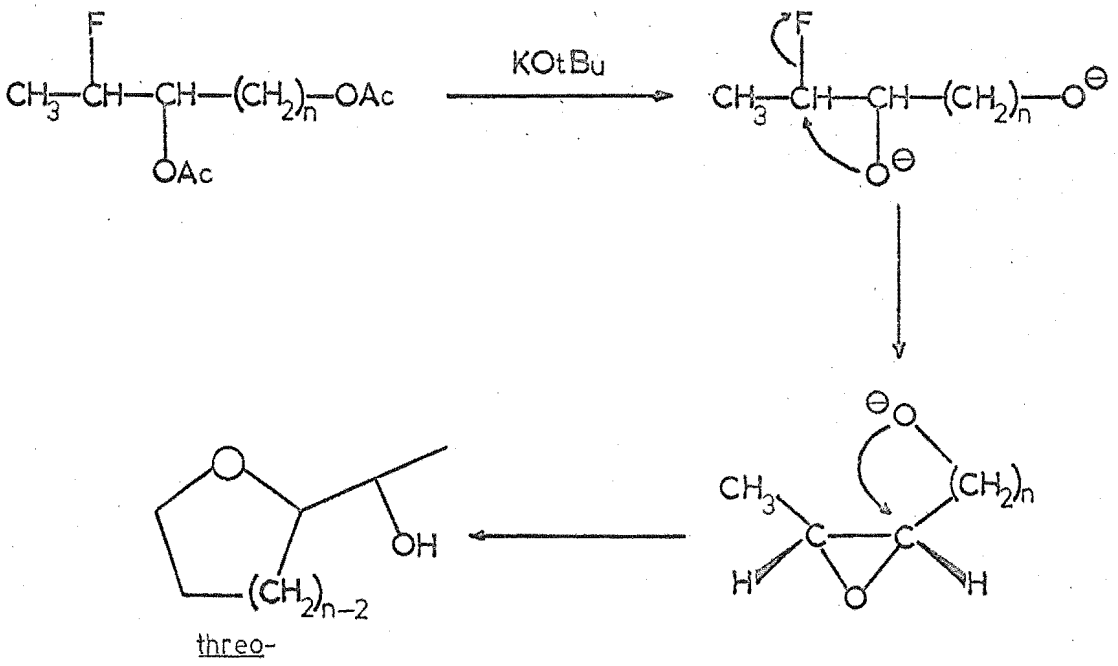


FIG 43

As this epoxide must be formed with inversion of configuration at the C-F carbon atom the original 5-fluoro-4-hydroxyhexan-1-ol acetate must be the threo-isomer (54). The stereochemistry of 4-fluoro-5-hydroxyhexan-1-ol acetate (61) cannot be so conclusively proved since there is the possibility that the fluorohydrin (61) was formed by fluoride ion attack with complete retention of configuration and that the primary alkoxide ion displaces the fluorine with inversion of

configuration to give the tetrahydrofuran derivative (38) without the intermediacy of the epoxide.

A similar type of argument, to that outlined above, for the fluorohydrins (59,65) obtained from the trans-epoxyacetate (25) shows that they have erythro-configuration.

Rearrangements of Epoxyheptanol Acetates (27,33)

The reactions of trans-5,6-epoxyheptan-1-ol acetate (27) with BF_3-etherate were carried out under similar conditions to those used for the epoxyhexanol acetates (25,31). However, in this case although carbonyl and fluorohydrin compounds were formed no tetrahydropyran or oxepane derivatives could be detected. The products and their absolute yields obtained from these reactions were: 5-acetoxy-2-methylpentanal (5%, 51), 7-acetoxyheptan-3-one (11%, 47), 7-acetoxyheptan-3-one (8%, 49), erythro-6-fluoro-5-hydroxyheptan-1-ol acetate (36%, 60) and erythro-5-fluoro-6-hydroxyheptan-1-ol acetate (35%, 63).

The reactions of cis-5,6-epoxyheptan-1-ol acetate (33) with BF_3-etherate under similar conditions to those used for the trans-isomer (27) yielded: 7-acetoxyheptan-3-one (35%, 47), threo-6-fluoro-5-hydroxyheptan-1-ol acetate (13%, 52) and threo-5-fluoro-6-hydroxyheptan-1-ol acetate (10%, 56).

The three carbonyl compounds (51,47,49) formed by the reactions of cis- and trans-epoxyacetates (27,33) with BF_3-etherate were isolated by preparative g.l.c. and their structures determined from their n.m.r. and i.r. spectra. Although the two ketones (47,49) are quite stable the aldehyde (51) rapidly polymerizes once it is concentrated.

Unlike their C_6 analogues both the erythro-fluorohydrins (60,63) could be isolated by preparative g.l.c. As these

compounds could be obtained pure their g.l.c. response factors were compared with those for the other reaction products (47, 49). It was found that, within experimental error, the response factors of the fluorohydrins (60,63) were the same as those for the carbonyl compounds. Such results give a firm foundation for the assumption that the response factors of the fluorohydrins (52,54,56,58,61,64), which could not be isolated, are similar to those of the other products formed from the same epoxyacetate.

Unfortunately the fluorohydrins (52,56) obtained from the cis-epoxyacetate (33) were not as stable as those formed from the trans-isomer (27) and were consequently isolated as their acetoxy derivatives (53,57).

The stereochemistry of the fluorohydrin isomers (52,56,60, 63) was proven by a similar method to that used for their C_6 analogues. The fluorohydrins or their acetoxy derivatives were reacted with potassium tert.-butoxide to give an epoxide intermediate (Fig. 42), which subsequently isomerised to give known products. The erythro-fluorohydrins (60,63) gave the same products as those produced when trans-epoxyacetate (27) was reacted with potassium tert.-butoxide while acetoxy derivatives of the threo-fluorohydrins (53,57) gave the same products as cis-epoxyacetate (33).

Rearrangements of ^{18}O Enriched Epoxyacetates (23,25)

The position in the final products of the ^{18}O oxygen label, which was originally in the ester carbonyl group of the epoxides (23,25), should give considerable information about the mechanism by which the isomerizations proceed. In order to obtain this information the ^{18}O enriched epoxyacetates (23,25) were synthesized by reacting ^{18}O acetyl chloride with trans-

pent-3-en-1-ol (7) and trans-hex-4-en-1-ol (9) and epoxidation of the resulting acetates (6,8) with monoperoxyphthalic acid in ether. The rearrangements of the $^{18}0$ enriched epoxides (23,25) were carried out in a similar fashion to those of the unlabelled compounds.

The methyltetrahydrofuranol acetate (46) obtained from the isomerization of labelled trans-3,4-epoxypentan-1-ol acetate (23) was shown by mass spectral analysis to contain 27.8% 0^{18}. However, the alcohol (45) obtained from the $LiAlH_4$ reduction of acetate (46) contained 25.2% $^{18}0$. Unfortunately, it was not possible by mass spectral methods to prove whether the labelled oxygen was incorporated in the tetrahydrofuran ring, or in the hydroxyl group, or even in both.

The acetoxyethyltetrahydrofuran compound (39) isolated from the acid catalysed reaction products of $^{18}0$ enriched trans-4,5-epoxyhexan-1-ol acetate (25) was shown to contain 27.1% $^{18}0$. On the other hand the alcohol (38) obtained from the $LiAlH_4$ reduction of the acetate (39) showed no isotope enrichment at all.

Mechanism of Formation of Tetrahydrofuranol Derivatives (43,46,37,39) from Epoxyacetates (23,25,29,31)

Any reaction pathway proposed for the acid catalysed isomerizations of epoxides (23,25,29,31) to tetrahydrofuran derivatives (43,46,37,39) must rationalize the following observations.

(a) the formation of products in which the original configurations of the epoxide carbon atoms are retained;

(b) why the 5,6-epoxy heptanol acetates (27,33) do not form cyclic ether products;

(c) the distribution of ^{18}O in the products obtained from isomerizations of the two isotope enriched epoxyacetates (23, 25), i.e. the alcohol (45) obtained by reduction of ^{18}O enriched cis-2-methyltetrahydrofuran-3-ol acetate (46) contained 92% of the possible amount of the labelled oxygen whereas the alcohol (36) obtained by reduction of ^{18}O enriched threo-2-(1-acetoxylethyl)tetrahydropyran (39) contained no isotopic label.

If a mechanism involving an intermediate similar to the oxabicyclobutonium ion (Fig. 39) postulated by Richey and Kinsman[69] were proposed for the isomerization of the epoxyacetates (23,25,29,31), the predicted stereochemistry of the products would be opposite to that found experimentally.

The reaction pathway which appears best able to explain the observed products from the rearrangements of the epoxyacetates (23,25,293,1) is one in which the ortho esters (75,76) are proposed as intermediates. Once formed these compounds have been shown[70] to undergo cleavage by Lewis acids such as boron trifluoride to form acetonium ions*, Fig. 44(b). Such cleavage occurring between any one of the three oxygen to acetyl carbon bonds. If an ortho ester (75,76) were cleaved at position 2 the intermediate would be reformed. However, if fission were to occur at position 1 then the Lewis acid coordinated alkoxide ion could displace the oxygen atom bonded to the γ carbon, Fig. 44.

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* Cleavage of the ortho ester intermediate by boron trifluoride with subsequent formation of the $BF_4^{\ominus}$ salt of one of the acetonium ions is probably responsible for the crystals that precipitate out of the concentrated reaction mixture (page 60). When the reaction was carried out with a lower boron trifluoride concentration such salts did not form.

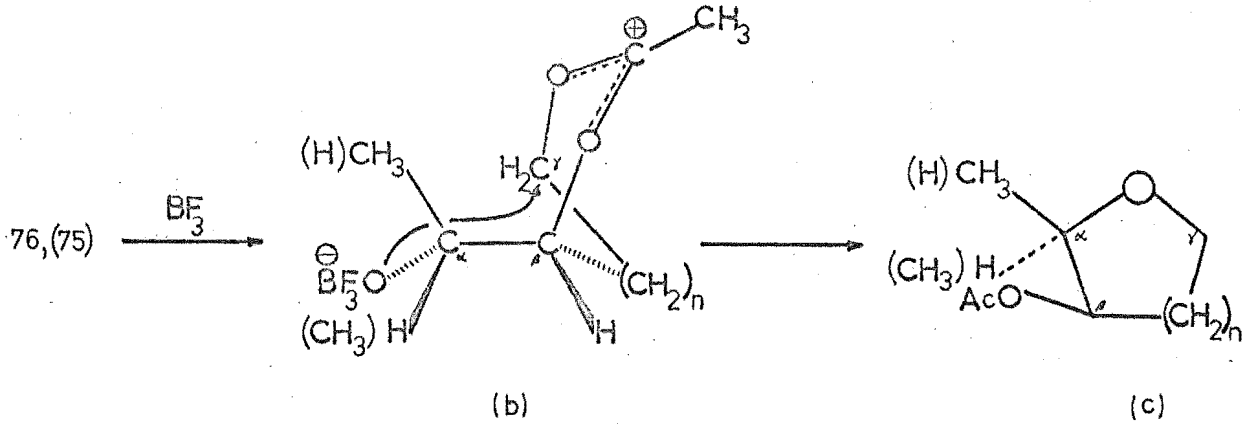

FIG 44

This process would give an n+4 membered cyclic ether product with the acetate group attached to the ring. On the other hand if carbon oxygen bond cleavage occurred at position 3 then the boron trifluoride coordinated alkoxide ion could displace the oxygen attached to the α or β carbon. Attack at the α carbon would give an n+4 membered cyclic ether product with the acetate group attached to the ring, Fig. 45.

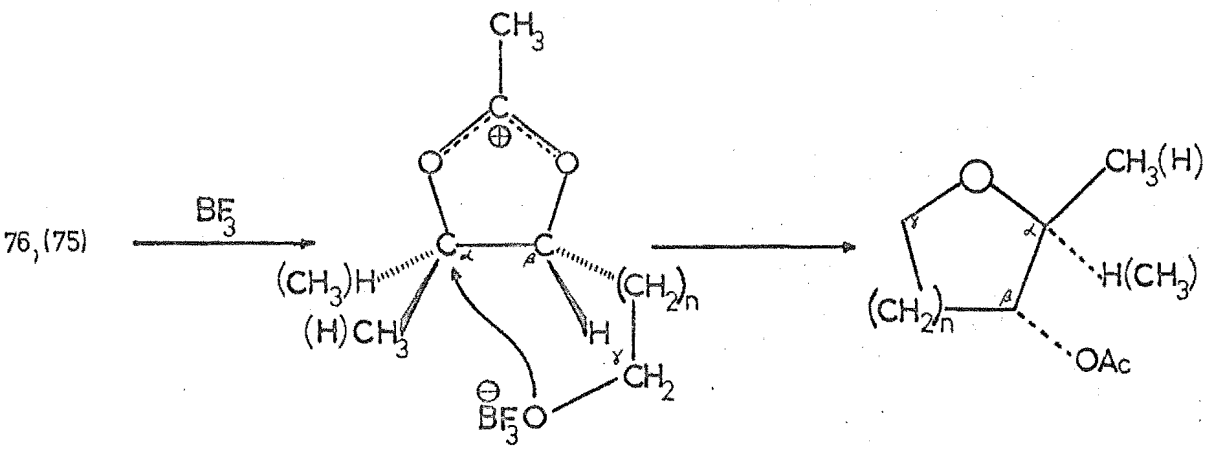

FIG 45

However, in this case the stereochemical relationship of the acetate and methyl groups would be opposite to that formed by cleavage at position 2 followed by attack at the γ carbon. Displacement of the oxygen attached to the β carbon would give an n+3 membered cyclic ether in which the acetate group is not

bonded to the ring, Fig. 46.

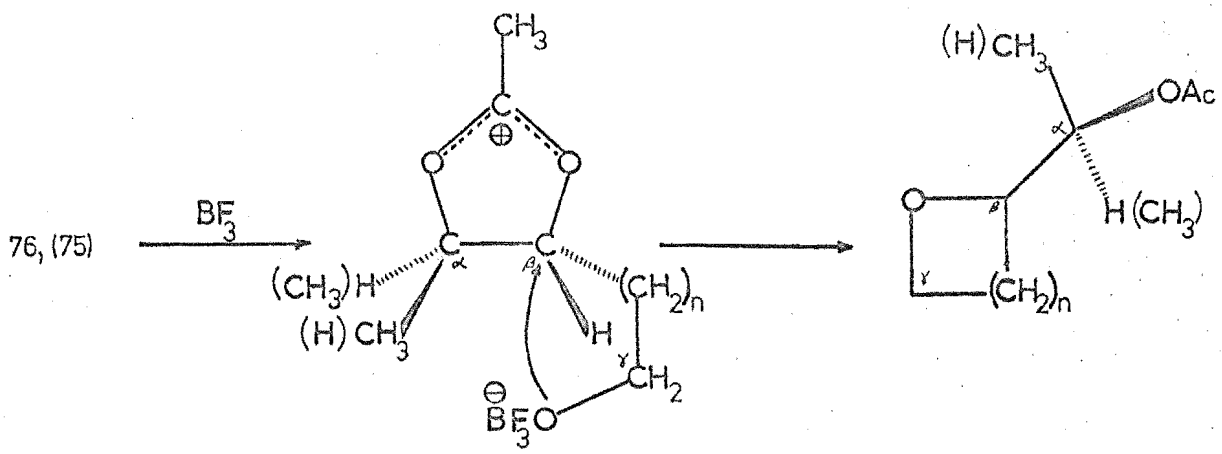

FIG 46

Formation of the ortho ester intermediates (75,76) from the epoxyacetates may occur by two different pathways. The first of these involves nucleophilic participation by the ester carbonyl group during the acid catalysed ring opening of the epoxide. Such participation would form an acetonium ion which would then react further with the Lewis acid coordinated oxygen atom to give an ortho ester, Figs 47,48.

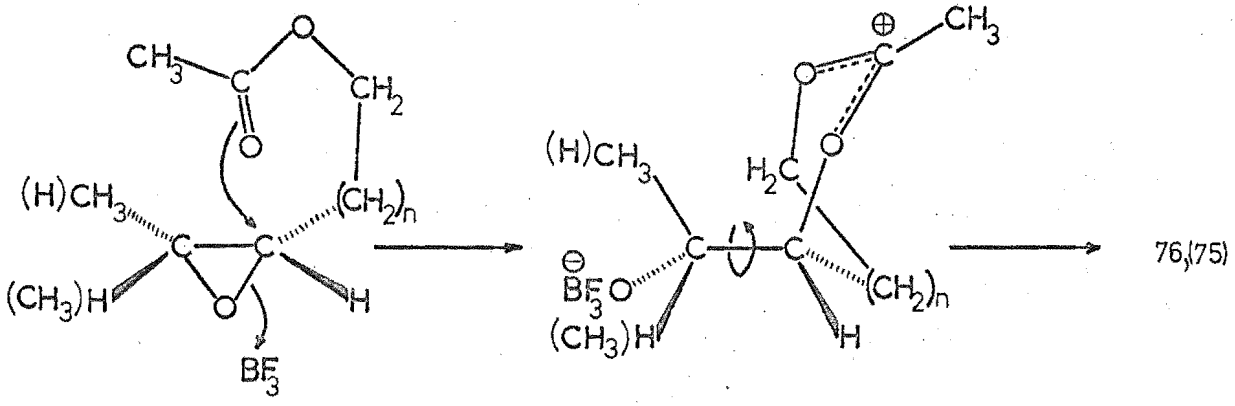

FIG 47

Although the ester carbonyl could attack at either of the two epoxide carbon atoms both pathways give the same ortho ester, i.e. trans-epoxyacetates (23,25) would give endo-substituted esters (75), while cis-epoxyacetates (29,31) would give exo-substituted esters (76).

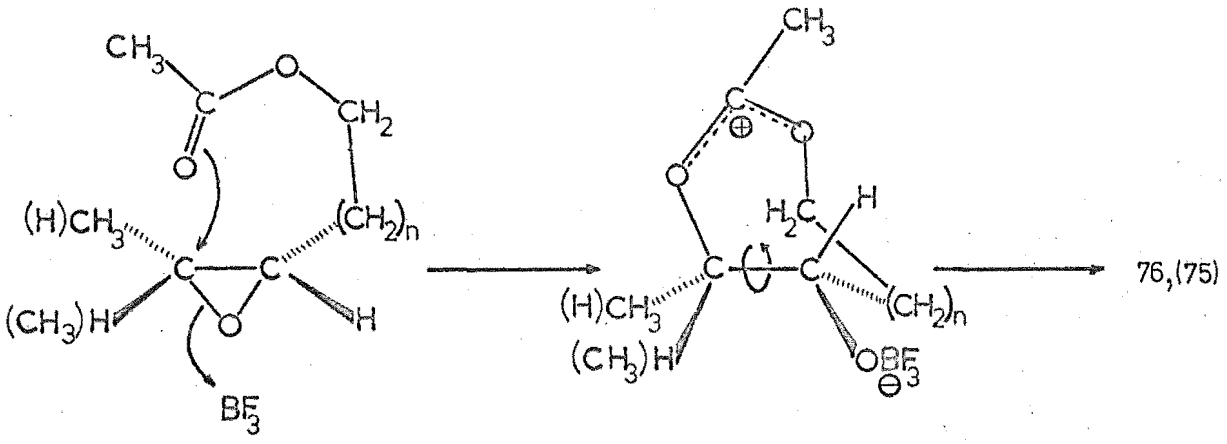

FIG 48

The second reaction pathway by which ortho esters (75,76) may be formed from epoxyacetates (23,25,29,31) is outlined in Figs 49,50.

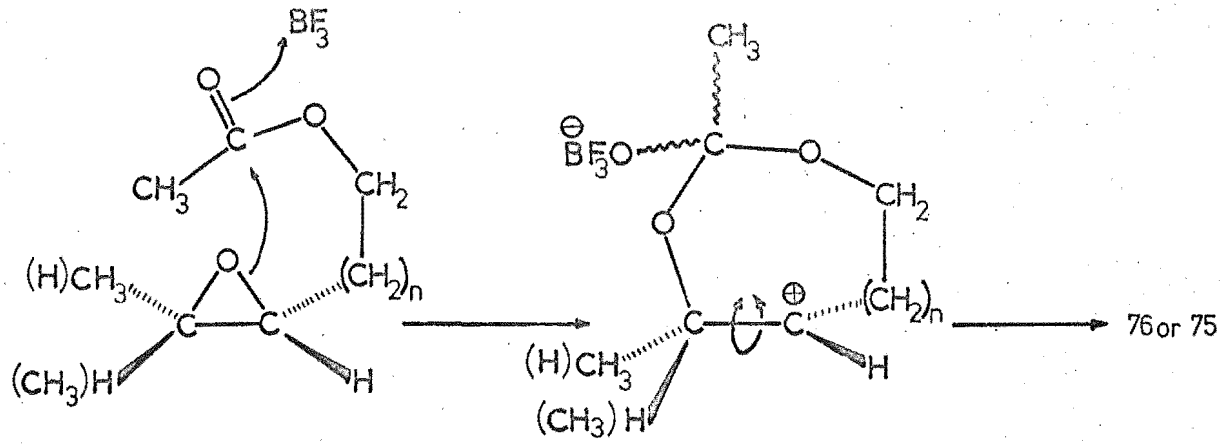

FIG 49

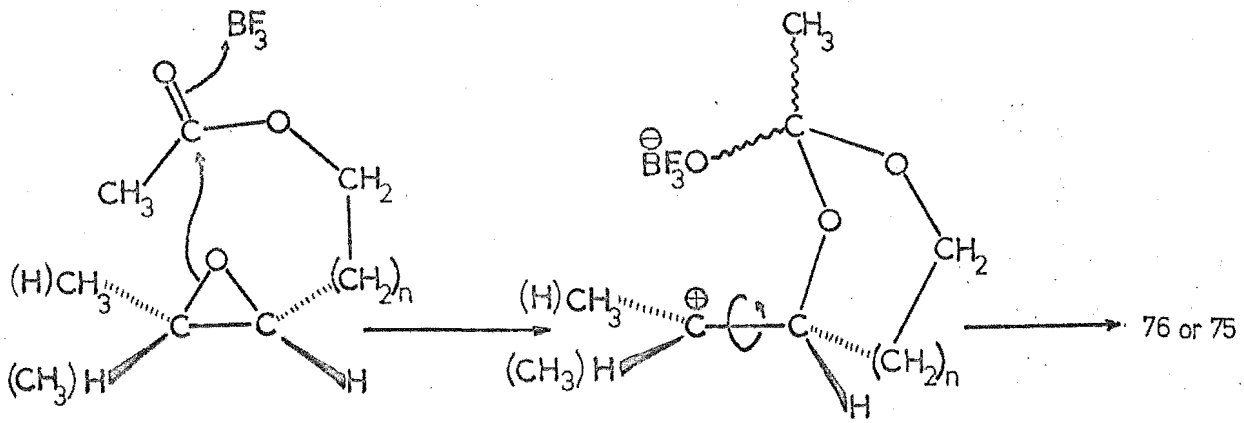

FIG 50

Nucleophilic attack of the ester carbonyl group by the epoxide oxygen is followed by reaction of the Lewis acid coordinated oxygen with the carbonium ion. If the epoxide ring were to open such that rotation about the secondary carbonium ion cannot occur (Fig. 49) then both cis- and trans-epoxyacetates (23,24,29,31) would give a mixture of exo- and endo-substituted ortho esters (75,76) depending on which side of the carbonyl group the epoxide oxygen attacked. If cleavage of the epoxide ring were to occur such that the carbonium ion is free to rotate (Fig. 50) both exo- and endo-substituted ortho esters (75,76) would be formed but probably with a bias towards the more stable isomer. Such mixtures of ortho ester intermediates would be expected to give mixtures of product diastereo-isomers.

The evidence presented above indicates that the mechanism of formation of the ortho esters (75,76) which most readily rationalizes the experimentally observed products is one in which neighbouring group participation of the ester carbonyl group occurs during epoxide ring opening, Figs 47,48. This mode of formation of the ortho ester is also in accord with the distribution of isotopically labelled oxygen in the products formed.

As trans-epoxyheptanol acetate (27) does not form cyclic ether products when reacted with BF_3-etherate, it appears that an eight or nine-membered acetonium ion ring is thermo-dynamically significantly less stable and/or its rate of formation is no longer competitive with the alternative reaction processes. It is likely therefore, that only the seven-membered acetonium ion ring (Fig. 47) would be formed from trans-epoxyhexanol acetate (25) and consequently that the

isotopically labelled ester carbonyl oxygen should appear bonded to the β carbon in the ortho ester (75b). Cleavage of this ortho ester at position 3 followed by nucleophilic displacement of the oxygen attached to the β carbon would give the 2-(1-acetoxyethyl)tetrahydrofuran (39) product with all the ^{18}O contained in the ester carbonyl group. Reduction of this acetate would then give an alcohol (38) with no isotope enrichment. This was found experimentally.

During acid catalysed reaction of trans-epoxypentanol acetate (23) the ester carbonyl group may participate to form either a six or a seven-membered acetonium ion ring. As a six-membered ring is more likely to form, most of the isotopic label should end up bonded to the β carbon atom in the ortho ester (75a). However, some of the ^{18}O would be expected to be bonded to the α carbon. This would mean that cleavage of the ortho ester at position 3 followed by nucleophilic attack at the α carbon (Fig. 45) should give methyltetrahydrofuranol acetate (46) with most of the labelled oxygen incorporated in the singly bonded ester oxygen atom and the remainder in the carbonyl group. Reduction of this acetate would give an alcohol (45) containing a considerable percentage of the possible amount of ^{18}O. The actual experimental values indicate that 8% of the ortho ester (75a) intermediate was formed via a seven-membered acetonium ion and the remainder via a six-membered one.

Mechanism of Formation of Fluorohydrins (61,60,64,63,54,52,58, 56) and Carbonyl Compounds (47,48,49,50,51) from Epoxyacetates (25,27,31,33)

During the BF_3-etherate catalysed reactions of the epoxyacetates (25,27,31,33) varying amounts of fluorohydrins (61,60, 64,63,54,52,58,56) and carbonyl compounds (47,48,49,50,51) were formed. The yield of these products rose rapidly as neighbouring group participation by the ester carbonyl function became more unfavourable.

The stereochemistry of all eight fluorohydrins indicates that these compounds have been formed with inversion of configuration at one of the epoxide carbons. Such inversion of stereochemistry is usual for nucleophilic attack during the acid catalysed ring opening of an epoxide and rules out the possibility that the fluorohydrins obtained from the epoxyhexanol acetates (25,31) were formed via an ortho ester intermediate.

As fluorohydrins have been implicated as intermediates in the rearrangements of epoxides such a possibility had to be ruled out for the compounds (61,60,64,63,54,52,58,56) obtained from the epoxyacetates (25,27,31,33). Only the fluorohydrins (60,63) from the reaction of trans-epoxyheptanol acetate (27) with BF_3-etherate could be isolated pure. However, when these compounds were subjected to similar conditions to those used for the isomerization of the epoxides no reaction was detected. Although the other fluorohydrins could not be isolated, it seems unlikely that they are intermediates as the product ratios obtained from the reaction of the epoxides (25,31,33) were not dependent on the reaction time. If the fluorohydrins are intermediates it would be expected that their yields would

decrease with time while the yields of other products increased.

The carbonyl compounds formed during the isomerization of the cis- and trans-epoxyacetates (31,27,33) are similar to those obtained from cis- and trans-epoxybutane. Approximately 20% of the product from the trans-epoxide (27) is an aldehyde (51) whereas the cis-epoxides (31,33) gave only ketones (47,48, 49,50). These products may be rationalized in terms of a similar carbonium ion intermediate to that used for the cis- and trans-epoxybutanes (page 22).

The fact that all the initial epoxide could not be accounted for by cyclic ether products (43,46) in the reactions of cis- and trans-epoxypentanol acetates (23,29), and yet only a trace of "carbonyl" compounds and no fluorohydrins could be detected suggests that fragmentation or polymerization processes are occurring. Although polymerization reactions cannot be ruled out, no evidence for such products was found. A fragmentation reaction (Fig. 51) following a similar pathway to that proposed for cis-epoxypentanol (Fig. 35) seems more likely with propanal and the enol acetate of acetaldehyde being formed. When the boron trifluoride was quenched the enol acetate ester would hydrolyse to acetaldehyde and the anion of acetic acid. Neither of these compounds would be detected as potassium acetate is insoluble in ether and acetaldehyde, being volatile, would distill off with the solvent.

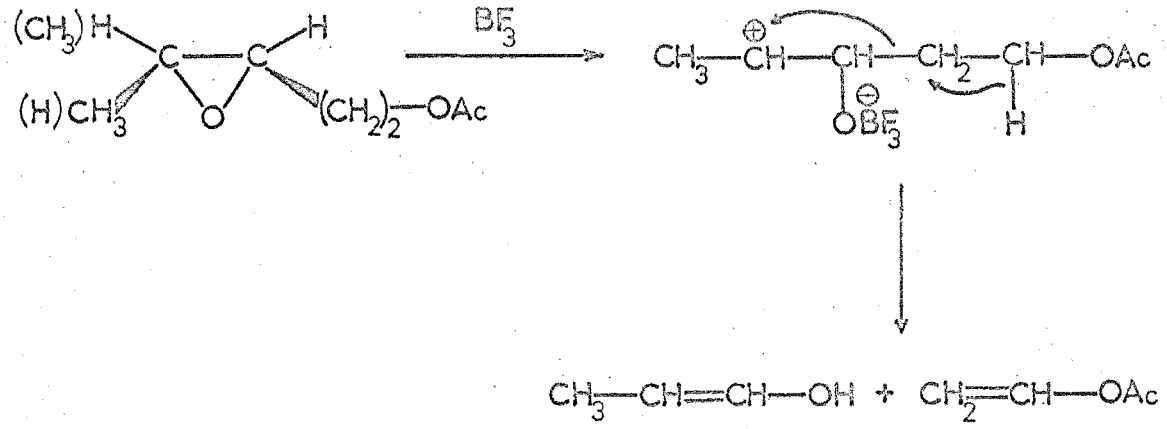
(CH3)H
H
(H)CH3
O
(CH2)2—OAc
BF3
CH3—CH—CH—CH2—CH—OAc
OBF3
H
CH3—CH=CH—OH + CH2=CH—OAc

FIG 51

EXPERIMENTAL

Infrared spectra were recorded on a Shimadzu IR27G spectrophotometer, and are for liquid films unless otherwise stated.

Nuclear magnetic resonance spectra were obtained on a Varian A60 spectrometer for $CDCl_3$ solutions with $CHCl_3$ and TMS as internal standards. NMR parameters are derived by first order analysis and confirmed wherever possible by double irradiation experiments.

Analytical gas chromatography was performed on an Aerograph 200 using 2% FFAP, SE30 and Carbowax 20M on Aeropak 30, in 1/8" stainless steel columns. Preparative g.l.c. was performed on a Varian Autoprep 705 using 7% FFAP and 20% SE30 on Chromosorb-W 80/100 (DMCS treated, acid washed) in 3/8" aluminium columns.

Fractional distillations were carried out using Nester-Faust annular teflon and spinning band columns.

Micro-analyses were determined at the University of Otago. Most mass spectra were recorded on an AEI Model M.S.901 spectrometer in the Chemistry Department, University of Canterbury, but some were very kindly run on a similar machine by Professor R. Hodges at Massey University.

3-Acetyldihydrofuran-2(3H)-one (1)

3-Acetyldihydrofuran-2(3H)-one is prepared by the method of Adams and VanderWerf[38]; b.p. 90°/1mm; ν_{max} 1770, 1720, 1362 cm^{-1}; n.m.r. δ 4.33 (triplet, 2H, $J_{5,4}$ 6.5 Hz; C5-H_2), 3.76 (quartet, 1H, $J_{3,4}$ 7.0 Hz, $J_{3',4'}$ 9.5 Hz; C3-H_1), 3.07-1.87 (multiplet, 2H; C4-H_2), 2.41 (singlet, 3H; CO-CH_3).

5-Chloropentan-2-one (2)

5-Chloropentan-2-one is prepared by the method of Cannon, Ellis and Leal[39]; b.p. 70-72°/20 mm; ν_{max} 1720, 1355 cm^{-1}; n.m.r. δ 3.58 (triplet, 2H, $J_{5,4}$ 6 Hz; C5-H_2), 2.65 (triplet, 2H, $J_{3,4}$ 6 Hz; C3-H_2), 2.16 (singlet, 3H; C1-H_3) 2.21-1.61 (multiplet, 2H; C4-H_2).

Cyclopropylmethyl ketone (3)

Cyclopropylmethyl ketone is prepared by the method of Cannon, Ellis and Leal[39]; b.p. 110-112°; ν_{max} 1705, 1380 cm^{-1}; n.m.r. δ 2.17 (singlet, 3H; C1-H_3), 2.13-1.67 (multiplet, 1H; C3-H_1), 1.05-0.67 (multiplet, 4H; C4-H_2, C5-H_2).

α-Methylcyclopropanemethanol (4)

α-Methylcyclopropanemethanol is prepared by the method of Julia, Julia and Tchen[40]; b.p. 122°; ν_{max} 3375 cm^{-1}; n.m.r. δ 3.05 (quintet, 1H, $J_{2,1}$ 6 Hz, $J_{2,3}$ 6 Hz; C2-H_1), 1.20 (doublet, 3H, $J_{1,2}$ 6 Hz; C1-H_3), 1.09-0.00 (multiplet, 5H; C3-H_1, C4-H_2, C5-H_2).

trans-1-Bromopent-3-ene (5)

trans-1-Bromopent-3-ene is prepared by the method of Julia, Julia and Tchen[40]. A mixture of cis- and trans-1-bromopent-3-enes(1:9) that could not be separated by distillation is obtained; b.p. 125°; ν_{max} 970 cm^{-1}; n.m.r. δ 5.90-5.08 (multiplet, 2H; C4-H_1), 3.30 (triplet, 2H, $J_{1,2}$ 7 H_z; C1-H_2), 2.83-2.25 (multiplet, 2H; C2-H_2), 1.65 (doublet, 3H, $J_{5,4}$ 4 Hz, $Wh/_2$ 3 Hz; C5-H_3).

trans-Pent-3-en-1-ol acetate (6)

trans-Pent-3-en-1-ol acetate is prepared by the method of Julia, Julia and Tchen[40]; b.p. 92°/100 mm; ν_{max} 1745, 1360, 965 cm^{-1}; n.m.r. δ 5.88-5.08 (multiplet, 2H, C4-H_1, C3-H_1), 4.05 (triplet, 2H, $J_{1,2}$ 7 Hz; C1-H_2), 2.50-2.10 (multiplet, 2H; C2-H_2), 2.02 (singlet, 3H; CO-CH_3), 1.63 (doublet, 3H, $J_{5,4}$ 4 Hz, $W_{\frac{1}{2}}$ 3 Hz; C5-H_3).

trans-3,4-Epoxypentan-1-ol acetate (23)

trans-Pent-3-en-1-ol acetate (1.28 gm, 6) is placed in a conical flask (250 ml) and monoperoxyphthalic acid (50 ml, 0.35M) is added. The flask is stoppered and kept at a temperature of approximately 5°C for one week.

The reaction is worked up by the addition of excess anhydrous potassium carbonate after which the solid is filtered off and the ether removed by distillation. The crude product is purified by preparative gas chromatography to give pure trans-3,4-epoxypentan-1-ol acetate (0.86 gm, 60%); ν_{max} 1745, 1360, 1350 cm^{-1}; n.m.r. δ 4.18 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.93-2.58 (multiplet, 2H; C4-H_1, C3-H_1), 2.12-1.65 (multiplet, 2H; C2-H_2), 2.03 (singlet, 3H; CO-CH_3), 1.28 (doublet, 3H, $J_{5,4}$ 5 Hz; C5-H_3). Found: C, 57.84; H, 8.60. $C_7H_{12}O_3$ requires C, 58.33; H, 8.35.

trans-Pent-3-en-1-ol (7)

trans-Pent-3-en-ol acetate (42 gm, 6) and potassium hydroxide (56 gm) are added to methanol (200 ml) and the mixture refluxed for an hour. The alcohol is extracted with ether, washed with dilute sulphuric acid, aqueous sodium bicarbonate and then dried with potassium carbonate. The ether is removed and the mixed alcohols (22 gm, 75%) distilled; b.p. 78-79/88 mm;

ν_{max} 3375, 965 cm^{-1}; n.m.r. δ 5.90-5.08 (multiplet, 2H; C4-H_1, C3-H_1), 3.60 (triplet, 2H, $J_{1,2}$ 6.5 Hz; C1-H_2), 2.47-2.05 (multiplet, 2H; C2-H_2), 1.67 (doublet, 3H, $J_{5,4}$ 4 Hz, $W_{\frac{1}{2}}$ 3 Hz; C5-H_3).

trans-3,4-Epoxypentan-1-ol (22)

trans-Pent-3-en-1-ol (1.72 gm, 7) is reacted with monoperoxyphthalic acid under the same conditions as trans-pent-3-en-1-ol acetate (6). After purification by preparative gas chromatography trans-3,4-epoxypentan-1-ol (1.3 gm, 64%) is obtained; ν_{max} 3450 cm^{-1}; n.m.r. δ 3.77 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2). 3.12-2.70 (multiplet, 2H; C3-H_1, C4-H_1), 2.03-1.53 (multiplet,2H; C2-H_2), 1.30 (doublet, 3H, $J_{5,4}$ 5 Hz; C5-H_3). The compound is hydroscopic and an accurate analysis could not be obtained. Measured: 102.067744. $C_5H_{10}O_2$ requires 102.068075.

Pent-3-yn-1-ol (12)

Pent-3-yn-1-ol is prepared by the method of Crombie and Harper[41] but with a yield of 13%; b.p. 154-157°; ν_{max} 3375 cm^{-1}; n.m.r. δ 3.67 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.55-2.20 (multiplet, 2H; C2-H_2), 1.78 (triplet, 3H, $J_{5,2}$ 2.5 Hz; C5-H_3).

cis-Pent-3-en-1-ol (16)

cis-Pent-3-en-1-ol is prepared by the method of Crombie and Harper[41]; ν_{max} 3350, 710 cm^{-1}; n.m.r. δ 5.91-5.10 (multiplet, 2H; C3-H_1, C4-H_1), 3.60 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.55-2.11 (multiplet, 2H; C2-H_2), 1.63 (doublet, 3H, $J_{5,4}$ 5 Hz, $W_{\frac{1}{2}}$ 3 Hz; C5-H_3).

cis-3,4-Epoxypentan-1-ol (28)

cis-Pent-3-en-1-ol (1 gm, 16) is epoxidized in a similar manner to trans-pent-3-en-1-ol acetate (6). After purification by preparative gas chromatography cis-3,4-epoxypentan-1-ol (0.63 gm, 53%) is obtained; ν_{max} 3425 cm^{-1}; n.m.r. δ 3.83 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 3.27-2.90 (multiplet, 2H; C3-H_1, C4-H_1), 2.00-1.53 (multiplet, 2H; C2-H_2), 1.28 (doublet, 3H, $J_{5,4}$ 5 Hz; C5-H_3); measured: 102.068477. $C_5H_{10}O_2$ requires 102.068075.

cis-3,4-Epoxypentan-1-ol acetate (29)

cis-Pent-3-en-1-ol (0.5 gm, 16) is dissolved in dry pyridine (2.5 ml) and acetic anhydride (0.6 gm) is added. The reaction mixture is then left overnight at room temperature. The next day ether is added and the pyridine removed by washing with 10% aqueous hydrochloric acid. The ether is removed by distillation and the crude residue is then epoxidized in a similar manner to trans-pent-3-en-1-ol acetate (6). After purification by preparative gas chromatography cis-3,4-epoxypentan-1-ol acetate (0.49 gm, 58%) is obtained; ν_{max} 1740, 1370, 1360 cm^{-1}; n.m.r. δ 4.22 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 3.27-2.83 (multiplet, 2H; C3-H_1, C4-H_1), 2.05 (singlet, 3H; Co-CH_3), 1.92 (quartet, 2H, $J_{2,1}$ 6 Hz, $J_{2,3}$ 5.5 Hz; C2-H_2), 1.28 (doublet, 3H, $J_{5,4}$ 5.5 Hz; C5-H_3); found: C, 58.14; H, 8.40, $C_7H_{12}O_3$ requires C, 58.33; H, 8.35.

3-Chloro-2-methyltetrahydropyran (21)

3-Chloro-2-methyltetrahydropyran is prepared by the method of Crombie and Harper[42]; b.p. 150-175°.

trans-Hex-4-en-1-ol (9)

trans-Hex-4-en-1-ol (9) is prepared by the method of Crombie and Harper[42]. A mixture of cis- and trans-hex-4-en-1-ols (1:19) that could not be separated by distillation is obtained; b.p. 58°/15 mm; ν_{max} 3350, 960 cm^{-1}; n.m.r. δ 5.68-5.32 (multiplet, 2H; C_4-H_1, C_5-H_1), 3.60 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.27-1.85 (multiplet, 2H; C_2-H_2), 1.85-1.30 (multiplet, 5H; C6-H_3, C3-H_2).

trans-4,5-Epoxyhexan-1-ol acetate (25)

trans-Hex-4-en-1-ol (2gm, 9) is acetylated and then epoxidized in the usual way. The epoxyacetate obtained after work up is purified by preparative gas chromatography in order to remove the cis- isomer. trans-4,5-Epoxyhexan-1-ol acetate (1.9 gm, 60%) is obtained; ν_{max} 1725, 1370, 1360 cm^{-1}; n.m.r. δ 4.10 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_3), 2.92-2.52 (multiplet, 2H; C4-H_1, C5-H_1), 2.02 (singlet, 3H; CO-CH_3), 1.97-1.40 (multiplet, 4H; C2-H_2, C3-H_2), 1.28 (doublet, 3H, $J_{6,5}$ 5 Hz; C6-H_3); Found: C, 60.68; H, 8.88. $C_8H_{14}O_3$ requires C, 60.76; H, 8.86.

trans-4,5-Epoxyhexan-1-ol (24)

Pure trans-4,5-epoxyhexan-1-ol acetate (1.0 gm, 25) is added to an aqueous methanol solution (1:3, 10 ml) of sodium hydroxide (5%) kept at -20°C in an ice/salt bath. The mixture is stirred for 40 minutes and then sodium bicarbonate (1.0 gm) and cold ether (50 ml) are added. The mixture is stirred for another 15 minutes and then filtered to remove the solids present. The ethereal solution is dried (Na_2SO_4) and the solvent taken off under vacuum on a rotary evaporator. The

residue is then purified by a molecular distillation to give i.r. and n.m.r. pure trans-4,5-epoxyhexan-1-ol (0.4 gm, 54%); ν_{max} 3425 cm^{-1}; n.m.r. δ 3.67 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 3.00-2.55 (multiplet, 2H; C4-H_1, C5-H_1), 1.95-1.47 (multiplet, 4H; C2-H_2, C3-H_2), 1.30 (doublet, 3H, $J_{6,5}$ 5 Hz; C6-H_3); Measured: 116.083503. $C_6H_{12}O_2$ requires 116.083724.

cis-Hex-4-en-1-ol (18)

trans-Hex-4-en-1-ol (30 gm, 9) is brominated, dehydrobrominated, and then reduced over Lindlar catalyst in a similar fashion to trans-pent-3-en-1-ol acetate (6). The alcohol is then purified by preparative gas chromatography to give pure cis-hex-4-en-1-ol (3.9 gm, 13%); ν_{max} 3350, 710 cm^{-1}; n.m.r. δ 5.82-5.12 (multiplet, 2H; C4-H_1,C5-H_1), 3.63 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2) 2.38-1.88 (multiplet, 2H; C2-H_2), 1.88-1.35 (multiplet, 5H; C3-H_2, C6-H_3).

cis-4,5-Epoxyhexan-1-ol acetate (31)

cis-Hex-4-en-1-ol (1 gm, 18) is acetylated and then epoxidized in the usual way. The epoxyacetate obtained after work up is purified by preparative gas chromatography to give pure cis-4,5-epoxyhexanol acetate (0.95 gm, 60%); ν_{max} 1740, 1375, 1350 cm^{-1}; n.m.r. δ 4.13 (triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 3.27-2.75 (multiplet, 2H; C4-H_1, C5-H_1), 2.03 (singlet, 3H; CO-CH_3), 2.00-1.38 (multiplet, 4H; C2-H_2, C3-H_2), 1.27 (doublet, 3H, $J_{6,5}$ 5 Hz; C6-H_3). Found: C, 60.70; H, 8.88. $C_8H_{14}O_3$ requires C, 60.76; H, 8.86.

cis-4,5-Epoxyhexan-1-ol (30)

Pure cis-4,5-epoxyhexan-1-ol acetate (1.0 gm, 31) is hydrolysed in a similar manner to trans-4,5-epoxyhexan-1-ol acetate (25). After a molecular distillation i.r. and n.m.r. pure cis-4,5-epoxyhexan-1-ol (0.4 gm, 54%); ν_{max} 3450 cm^{-1}; n.m.r. δ 3.68 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 3.30-2.78 (multiplet, 2H; C4-H_1, C5-H_1), 2.00-1.45 (multiplet, 4H; C2-H_2, C3-H_2), 1.27 (doublet, 3H, $J_{6,5}$ 5 Hz; C6-H_3); Measured: 116.083625. $C_6H_{12}O_2$ requires 116.083724.

trans-Hept-5-en-1-ol (11)

trans-Hept-5-en-1-ol was prepared by the method of Dreger[43]. After distillation on a spinning band column a mixture of cis- and trans-hept-5-en-1-ols (1:9) are obtained; ν_{max} 3340, 960 cm^{-1}; n.m.r. δ 5.75-4.97 (multiplet, 2H; C5-H_1, C6-H_1), 3.50 (triplet, 2H, $J_{1,2}$ 6 Hz, C1-H_2), 2.20-1.77 (multiplet, 2H; C2-H_2), 1.77-1.17 (multiplet, 7H; C3-H_2, C7-H_3).

trans-5,6-Epoxyheptan-1-ol acetate (27)

trans-Hept-5-en-1-ol (2gm, 11) is acetylated and then epoxidized in the usual way. The epoxyacetate obtained after work up is purified by preparative gas chromatography in order to remove the cis-isomer. trans-5,6-Epoxyheptan-1-ol acetate (1.8 gm, 60%) is obtained; ν_{max} 1740, 1370, 1355 cm^{-1}; n.m.r. δ 4.07 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.94-2.50 (multiplet, 2H; C4-H_1, C6-H_1), 2.05 (singlet, 3H; CO-CH_3), 1.83-1.43 (multiplet, 6H, C2-H_2, C3-H_2, C4-H_2), 1.28 (doublet, 3H, $J_{7,6}$ 5 Hz; C7-H_3); Found: C, 62.95; H, 9.30. $C_6H_{16}O_3$ requires C, 62.79; H, 9.30.

trans-5,6-Epoxyheptan-1-ol (26)

Pure trans-5,6-epoxyheptan-1-ol (1.0 gm, 27) is hydrolyxed in a similar way to trans-4,5-epoxyhexan-1-ol acetate (25). After a molecular distillation i.r. and n.m.r. pure trans-5,6-epoxyheptan-1-ol (0.38 gm, 50%) is obtained; ν_{max} 3450 cm^{-1}; n.m.r δ 3.63 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.98-2.53 (multiplet, 2H; C5-H_1, C6-H_1), 1.75-1.42 (multiplet, 6H; C2-H_2, C3-H_3, C4-H_4), 1.28 (doublet, 3H, $J_{7,6}$ 5 Hz; C7-H_3); Measured: 130.099636. $C_7H_{14}O_2$ requires 130.099373.

cis-Hept-5-en-1-ol (20)

trans-Hept-5-en-1-ol (30 gm, 11) is brominated, dehydrobrominated, and then reduced over Lindlar catalyst in a similar fashion to trans-pent-3-en-1-ol acetate (6). The alcohol is then purified by preparative gas chromatography to give pure cis-hept-5-en-1-ol (2.8 gm, 9%); ν_{max} 3350, 710 cm^{-1}; n.m.r. δ 5.82-4.93 (multiplet, 2H; C5-H_1, C6-H_1), 3.65 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.42-1.86 (multiplet, 2H; C2-H_2), 1.77-1.10 (multiplet, 7H; C3-H_2, C4-H_2, C7-H_3).

cis-5,6-Epoxyheptan-1-ol acetate (33)

cis-Hept-5-en-1-ol (1 gm, 20) is acetylated and then epoxidized in the usual way. The epoxyacetate obtained after work up is purified by preparative gas chromatography to give cis-5,6-epoxyheptanol acetate (0.90 gm, 60%), ν_{max} 1740, 1380, 1365 cm^{-1}; n.m.r. δ 4.09 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 3.23-2.73 (multiplet, 2H; C5-H_1, C6-H_1), 2.03 (singlet, 3H; CO-CH_3), 1.97-1.40 (multiplet, 6H, C2-H_2; C3-H_2, C4-H_2), 1.27 (doublet, 3H, $J_{7,6}$ 5 Hz; C7-H_3). Found: C, 62.75; H, 9.30. $C_9H_{16}O_3$ requires C, 62.79; H, 9.30.

cis-5,6-Epoxyheptan-1-ol (32)

Pure cis-5,6-epoxyheptan-1-ol acetate (1.0 gm, 33) is hydrolysed in a similar way to trans-4,5-epoxyhexan-1-ol acetate (25). After a molecular distillation i.r. and n.m.r. pure cis-5,6-epoxyheptan-1-ol (0.38 gm, 50%) is obtained; ν_{max} 3425 cm^{-1}; n.m.r. δ 3.65 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 3.25-2.75 (multiplet, 2H; C5-H_1, C6-H_1); 1.82-1.42 (multiplet, 6H; C2-H_2, C3-H_2, C4-H_2), 1.27 (doublet, 3H, $J_{7,6}$ 5 Hz; C7-H_3). Measured: 130.099480. $C_7H_{14}O_2$ requires 130.099373.

Rearrangement of trans-5,6-epoxyheptan-1-ol (26) with BF_3-etherate in ether

The rearrangement of the epoxide (26) is carried out in duplicate. To two oven dried conical flasks sodium dried ether (125 ml, 100 ml) and epoxide (26) (126.7 mg, 98.3 mg) are added. The mixtures are stirred with a magnetic stirrer and BF_3-etherate (450 mg, 360 mg) added. The reactions are allowed to proceed for two hours at room temperature and then quenched with saturated potassium carbonate solution (0.5 ml, 0.5 ml). After a further fifteen minutes stirring mesitylene (57.0 mg, 41.0 mg) and anhydrous potassium carbonate are added. The solids are then removed by filtration and the ether by careful distillation. The crude product is shown (g.l.c. using the mesitylene as a standard) to contain erythro 2-(1-hydroxyethyl)tetrahydropyran (95%, 34) and an unidentified compound which was probably trans-2-methyloxepan-3-ol (ca. 3%, 70).

erythro-2-(1-Hydroxyethyl)tetrahydropyran (34)

The epoxide (1 gm, 26) is rearranged and worked up in the usual way. The major product erythro-2-(1-hydroxyethyl)tetrahydropyran is purified by preparative gas chromatography; ν_{max} (CCl_4) 3634, 3588 cm^{-1}; n.m.r. δ 4.20-3.05 (multiplet, 4H; C2-H_1, C2-methine, C6-H_2), 2.00-1.30 (multiplet, 6H; C3-H_2, C4-H_2, C5-H_2), 1.12 (doublet, 3H, $J_{CH_3,CH}$ 6 Hz; COH-CH_3).

Rearrangement of cis-5,6-epoxyheptan-1-ol (32) with BF_3-etherate in ether

The rearrangement of the epoxide (32) is carried out, in duplicate, under the same reaction conditions as that of trans-5,6-epoxyheptan-1-ol (26). The crude product is shown (g.l.c. using mesitylene as a standard) to contain threo-2-(1-hydroxyethyl)tetrahydropyran (98%, 35). No other products were detected by g.l.c.

threo-2-(1-Hydroxyethyl)tetrahydropyran (35)

The epoxide (0.3 gm, 32) is rearranged and worked up in the usual way. The major product threo-2-(1-hydroxyethyl)tetrahydropyran is purified by preparative gas chromatography. ν_{max} (CCl_4) 3578 cm^{-1}; n.m.r. δ 4.23-2.87 (multiplet, 4H; C2-H_1, C2-methine, C6-H_2), 2.05-1.23 (multiplet, 6H; C3-H_2, C4-H_2, C5-H_2), 1.12 (doublet, 3H, $J_{CH_3,CH}$ 6 Hz; COH-CH_3).

Rearrangement of trans-4,5-epoxyhexan-1-ol (24) with BF_3-etherate in ether

The rearrangement of the epoxide (24) is carried out, in duplicate, under the same reaction conditions as that of trans-5,6-epoxyheptan-1-ol (26). The crude product is shown (g.l.c. using mesitylene as a standard) to contain erythro-2-(1-hydroxy-

ethyl)tetrahydrofuran (84%, 36) and trans-2-methyltetrahydropyran-3-ol (16%, 40). No other products are detected by g.l.c.

erythro-2-(1-Hydroxyethyl)tetrahydrofuran (36)[44] and trans-2-methyltetrahydropyran-3-ol (40)

trans-Hex-4-en-1-ol (1 gm, 9) is reacted with an ethereal solution of monoperoxyphthalic acid under the usual conditions. After work up in the normal way the products and their yields are very similar to those obtained from the BF_3-etherate rearranged trans-4,5-epoxyhexan-1-ol (24). The two products are purified by preparative gas chromatography to give: erythro-2-(1-hydroxyethyl)tetrahydrofuran; ν_{max} (CCl_4) 3560, 3588 cm^{-1}; n.m.r. δ 4.12-3.50 (multiplet, 3H; C2-H_1, C2-methine, C5-H_2), 2.03-1.67 (multiplet, 4H; C3-H_2, C4-H_2), 1.13 (doublet, 3H, $J_{CH_3,CH}$ 6 Hz; COH-CH_3); trans-2-methyltetrahydropyran-3-ol ν_{max} 3425 cm^{-1}; n.m.r. δ 4.05-2.87 (multiplet, 4H; C2-H_1, C3-H_1, C6-H_2), 2.24-1.00 (multiplet, 4H; C4-H_2, C5-H_2), 1.27 (doublet 3H, J_{2,CH_3} 6 Hz; C2-methyl).

trans-2-Methyltetrahydropyran-3-ol acetate (41)

trans-2-Methyltetrahydropyran-3-ol (0.1 gm, 40) is acetylated and worked up in the usual fashion. The crude product is purified by preparative gas chromatography to give pure trans-2-methyltetrahydropyran-3-ol acetate (81 mg, 60%); ν_{max} 1740, 1360 cm^{-1}; n.m.r. δ 4.47 (multiplet, 1H, $J_{3,2}$ 11 Hz, $J_{3',4'}$ 5 Hz; C3-H_1; decoupled with +127 Hz), 4.13-3.05 (multiplet, 3H, C2-H_1, C6-H_2), 2.35-1.28 (multiplet, 3H, C4-H_2, C5-H_2), 2.03 (singlet, 3H; CO-CH_3), 1.17 (doublet, 2H, J_{2,CH_3} 6 Hz; C2-methyl).

Rearrangement of cis-4,5-epoxyhexan-1-ol (30) with BF_3-etherate in ether

The rearrangement of the epoxide (30) is carried out in duplicate, under the same reaction conditions as that of trans-5,6-epoxyheptan-1-ol (26). The crude product is shown (g.l.c. using mesitylene as a standard) to contain threo-2-(1-hydroxyethyl)tetrahydrofuran (97%, 38). No other products are detected by g.l.c.

threo-2-(1-Hydroxyethyl)tetrahydrofuran (38)[44]

cis-Hex-4-en-1-ol (0.3 gm, 18) is reacted with an ethereal solution of monoperoxyphthalic acid under the usual conditions. After work up in the normal way the sole product, which is purified by gas chromatography, is threo-2-(1-hydroxyethyl)tetrahydrofuran; ν_{max} (CCl_4) 3586 cm^{-1}; n.m.r. δ 3.98-3.62 (multiplet, 4H; C2-H_1, C2-methine, C5-H_2), 2.16-1.47 (multiplet, 4H; C3-H_2, C4-H_2), 1.15 (doublet, 3H, J_{CH_3CH} 6 Hz; $COH-CH_3$).

Rearrangement of trans-3,4-epoxypentan-1-ol (22) with BF_3-etherate in ether

The rearrangement of the epoxide (22) is carried out, in duplicate, under similar reaction conditions to that of trans-5,6-epoxyheptan-1-ol (26) except that in this case the internal standard is cyclohexanol. The crude product is shown (g.l.c.) to contain cis-2-methyltetrahydrofuran-3-ol (8%, 45), trans-2-methyltetrahydrofuran-3-ol (86%, 42) and two unidentified high retention time products, possibly fluorohydrins (ca. 2%, ca. 4%).

cis- and trans-2-Methyltetrahydrofuran-3-ol (45 and 42)[45].

trans-3,4-Epoxypentan-1-ol (2 gm, 22) is rearranged and worked up in the usual way. The crude reaction product is purified by preparative gas chromatography to give: trans-2-methyltetrahydrofuran-3-ol; ν_{max} 3425 cm^{-1}; n.m.r. δ 4.13-3.63 (multiplet, 4H, C2-H_1, C3-H_1, C5-H_2), 2.50-1.55 (multiplet, 2H; C4-H_2), 1.18 (doublet, 3H, $J_{CH_3,2}$ 6 Hz; C2-methyl) and cis-2-methyltetrahydrofuran-3-ol; ν_{max} 3425 cm^{-1}; n.m.r. δ 4.28-3.52 (multiplet, 4H; C2-H_1, C3-H_1, C5-H_2), 2.47-1.72 (multiplet, 2H; C4-H_2), 1.25 (doublet, 3H, $J_{CH_3,2}$ 5 Hz; C2-methyl).

Dihydro-2-methylfuran-3(2H)-one (44)[46]

The mixed cis- and trans-isomers of 2-methyltetrahydrofuran-3-ol (1 gm, 42) are oxidized with Jones[47] reagent. The product is extracted with ether and purified by preparative gas chromatography to give dihydro-2-methylfuran-3(2H)-one (0.53 gm, 54%); ν_{max} 1760 cm^{-1}; n.m.r. δ 4.53-3.97 (multiplet, 2H; C5-H_2), 3.77 (quartet, 1H, J_{2,CH_3} 7 Hz; C2-H_1), 2.67-2.33 (multiplet, 2H; C4-H_2), 1.25 (doublet, 3H, $J_{CH_3,2}$ 7 Hz; C2-methyl).

Moist sodium reduction of dihydro-2-methylfuran-3(2H)-one (44)[48,49]

Dihydro-2-methylfuran-3(2H)-one (1.0 gm) is dissolved in ether (25 ml) and water (5 ml) is added. Clean sodium wire (2.3 gm) is added rapidly, the reaction being kept under control be external cooling. After all the sodium has reacted the product is extracted with additional ether which is washed with dilute HCl and dried with K_2CO_3. The ether is removed by distillation and the ratio of the cis- to trans-2-methyltetrahydrofuran-3-ols (12%, 45; 88%, 42) calculated by g.l.c.

Rearrangement of cis-3,4-epoxypentan-1-ol (28) with BF_3-etherate in ether

The rearrangement of the epoxide (28) is carried out, in duplicate, under the same conditions to that of trans-3,4-epoxypentan-1-ol (22). The crude product is shown (g.l.c.) to contain cis-2-methyltetrahydrofuran-3-ol (ca. 3%, 45), trans-2-methyltetrahydrofuran-3-ol (35%, 42) and two unidentified high retention time products, possibly fluorohydrins (9%, 16%).

Rearrangement of trans-3,4-epoxypentan-1-ol (22) with toluene-p-sulphonic acid in ether

The rearrangement of the epoxide (22) is carried out in a similar fashion to the BF_3-etherate reactions but using an equivalent amount of toluene-p-sulphonic acid (4.7 gm/l) that has been dried by azeotropic distillation with benzene, instead of the Lewis acid. The reaction is worked up in the usual manner and the ratio of cis- (45) to trans-2-methyltetrahydrofuran-3-ol (40) is shown (g.l.c.) to be 55:45. No other major products are detectable by g.l.c.

Rearrangement of cis-3,4-epoxypentan-1-ol (28) with toluene-p-sulphonic acid in ether

The rearrangement of the epoxide (28) with toluene-p-sulphonic acid is carried out in a similar fashion to that of trans-3,4-epoxypentan-1-ol (22). The crude product is shown (g.l.c.) to have a cis-(45) to trans-2-methyltetrahydrofuran-3-ol (40) ratio of 1:10. No other major products are detectable by g.l.c.

Rearrangement of trans-3,4-epoxypentan-1-ol (22) with trifluoroacetic acid in ether

The rearrangement of the epoxide (22) is carried out in a similar fashion to the BF_3-etherate reactions but using an equivalent amount of trifluoroacetic acid (2.9 gm/l) instead of the Lewis acid. The reaction is worked up in the usual manner and the ratio of cis-(45) to trans 2-methyltetrahydrofuran-3-ol (40) is shown (g.l.c.) to be 1:10. No other major products are detectable by g.l.c.

Rearrangement of cis-3,4-epoxypentan-1-ol (28) with trifluoroacetic acid in ether

The rearrangement of the epoxide (28) with trifluoroacetic acid is carried out in a similar fashion to that of trans-3,4-epoxypentan-1-ol (22). The crude product is shown (g.l.c.) to have a cis-(45) to trans-2-methyltetrahydrofuran-3-ol (40) radio of 1:8. Two other unidentified products of 9% and 26% of the total amount detectable by g.l.c. are found.

Rearrangement of trans-3,4-epoxypentan-1-ol (22) with BF_3-etherate in benzene

The rearrangement of the epoxide (22) is carried out in duplicate. To two oven dried conical flasks sodium dried benzene (130 ml, 107.1 mg) are added. The mixtures are stirred with a magnetic stirrer and BF_3-etherate (26 mg, 21 mg) added. The reactions are allowed to proceed for one and a half hours at room temperature, quenched with aqueous potassium carbonate, and then worked up in the usual manner after cyclohexanol (116.0 mg, 74.2 mg) has been added. The crude product is shown (g.l.c. using the cyclohexanol as a standard) to contain cis-2-methyltetrahydrofuran-3-ol (ca. 3%,

45) and trans-2-methyltetrahydrofuran-3-ol (30%, 40). No other major products are detectable by g.l.c.

Rearrangement of cis-3,4-epoxypentan-1-ol (28) with BF_3-etherate in benzene

The rearrangement of the epoxide (28) is carried out, in duplicate, under the same reaction conditions as that of trans-3,4-epoxypentan-1-ol (22). The only product that is shown (g.l.c.) to be present is a trace of trans-2-methyltetrahydrofuran-3-ol (40).

Rearrangement of trans-3,4-epoxypentan-1-ol (22) with BF_3-etherate in dichloromethane

Dichloromethane (80 ml) and epoxide (22) (78.0 mg) are added to an oven dried conical flask. The mixture is stirred with a magnetic stirrer and BF_3-etherate (15 mg) added. The reaction is allowed to proceed for one and a half hours at room temperature and then quenched with aqueous potassium carbonate. Cyclohexanol (60 mg) is added and the mixture is then worked up in the usual manner. The crude product is shown (g.l.c. using cyclohexanol as a standard) to contain a trace of cis-2-methyltetrahydrofuran-3-ol (45) and trans-2-methyltetrahydrofuran-3-ol (20%, 40). No other major products are detectable by g.l.c.

Rearrangement of cis-3,4-epoxypentan-1-ol (28) with BF_3-etherate in dichloromethane

The rearrangement of the epoxide (28) is carried out under the same reaction conditions as that of trans-3,4-epoxypentan-1-ol. The only product that is shown (g.l.c.) to be present is a trace of trans-2-methyltetrahydrofuran-3-ol (40).

But-1-en-3-ol (72)

Methylvinyl ketone (2 gm, 71) is dissolved in sodium dried ether (80 ml) and $LiAlH_4$ (0.5 gm) added. The mixture is then refluxed for one hour and the excess $LiAlH_4$ destroyed by hydrated sodium sulphate. The solids are then filtered off and the ether removed by distillation. A g.l.c. trace of the reaction mixture shows that two major products are present in a 2:1 ratio and the minor product has the same retention time as authentic butan-2-ol. Isolation of the major product by preparative gas chromatography gives but-1-en-3-ol (32%, 72); ν_{max} 3375, 920 cm^{-1}; n.m.r. δ 6.20-5.60 (multiplet, 1H; C2-H_1) 5.40-4.88 (multiplet, 2H; C1-H_2), 4.28 (quintet, 1H, $J_{3,2}$ 6.5 Hz, $J_{3,4}$ 6.5 Hz, C3-H_1), 1.25 (doublet, 3H, $J_{4,3}$ 6.5 Hz, C4-H_3).

Rearrangement of cis-5,6-epoxyheptan-1-ol acetate (33) with BF_3-etherate in ether

The rearrangement of the epoxide (33) is carried out in duplicate. To two oven dried conical flasks sodium dried ether (120 ml, 120 ml) and epoxide (33) (120.2 mg, 122.1 mg) are added. The mixtures are stirred with a magnetic stirrer and BF_3-etherate (960 mg, 960 mg) added in three equal portions over a period of two hours. The reactions are allowed to proceed for twenty-four hours at room temperature and then quenched with saturated potassium carbonate solution (1 ml, 1 ml). After a further fifteen minutes tetrahydrofurfuryl alcohol acetate (36.6 mg, 34.7 mg) and anhydrous potassium carbonate are added. The solids are removed by filtration and the ether by careful distillation. The crude product is shown (g.l.c. using the tetrahydrofurfuryl alcohol acetate as a standard) to contain: 7-acetoxyheptan-3-one (35%, 57), 7-acetoxyheptan-2-one (25%, 49), threo-6-fluoro-5-hydroxyheptan-

1-ol acetate (13%, 52) and threo-5-fluoro-6-hydroxyheptan-1-ol acetate (10%, 56).

Isolation of reaction products from BF_3-etherate rearrangement of cis-epoxyheptan-1-ol acetate (33)

The epoxide (1 gm, 33) is rearranged and worked up in the usual way. As both of the fluorohydrins (52,56) decompose during preparative gas chromatography they are converted to their acetates (53,57) first by reaction with acetyl chloride in pyridine. The pure compounds in order of their elution from the preparative gas chromatography column are: 7-acetoxy-heptan-3-one (47); ν_{max} 1740, 1718, 1350 cm^{-1}; n.m.r. δ 4.05 (poorly resolved triplet, 2H, $J_{7,6}$ 6 Hz; C7-H_2), 2.65-2.22 (multiplet, 4H; C2-H_2, C4-H_2), 2.03 (singlet, 3H; CO-CH_3), 1.78-1.45 (multiplet, 4H; C5-H_2, C6-H_2), 1.05 (triplet, 3H, $J_{1,2}$ 7 Hz; C1-H_3). Found: C, 62.70; H, 9.31. $C_9H_{16}O_3$ requires C, 62,79; H, 9.30. 7-Acetoxy-heptan-2-one (40; ν_{max} 1740, 1718, 1350 cm^{-1}; n.m.r. δ 4.03 (triplet, 2H, $J_{7,6}$ 6 Hz; C7-H_2), 2.43 (triplet, 2H, $J_{3,4}$ 6 Hz; C3-H_2), 2.13 (singlet, 3H; C1-H_3), 2.03 (singlet, 3H; CO-CH_3), 1.90-1.17 (multiplet, 6H; C4-H_2, C5-H_2, C6-H_2). Found: C, 62.75; H, 9.28. $C_9H_{16}O_3$ requires C, 62.79; H, 9.30. threo-5-Acetoxy-6-fluoroheptan-1-ol acetate (53); ν_{max} 1740, 1355 cm^{-1}; n.m.r. δ 4.93 (multiplet 1H, $J_{5,F}$ ca. 17 Hz, $J_{5,6}$ ca. 4 Hz, $J_{5,4}$? Hz; C5-H_1; decouples at ca. +181 Hz), 4.67 (multiplet, 1H, $J_{6,F}$ ca. 49 Hz, $J_{6,7}$ 6 Hz, $J_{6,5}$ ca. 4 Hz; C6-H_1; decouples at +213 Hz and +189 Hz), 4.05 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.10 (singlet, 3H; C5-CO-CH_3), 2.02 (singlet, 3H; CO-CH_3), 1.92-1.10 (multiplet, 6H; C2-H_2, C3-H_2, C4-H_2), 1.28 (multiplet, 3H, $J_{7,F}$ 24 Hz, $J_{7,6}$ 6 Hz; C7-H_3; decouples at -213 Hz and -189 Hz,

i.e. $J_{6,F}$, $J_{7,5}$ are of the same sign). Found: C, 56.11; H, 8.20; F, 8.63. $C_{11}H_{19}F_1O_4$ requires: C, 56.41; H, 8.11. threo-6-Acetoxy-5-fluoroheptan-1-ol acetate (57; ν_{max} 1740, 1355 cm^{-1}; n.m.r. δ 5.00 (multiplet, 1H, $J_{6,F}$ ca. 22 Hz, $J_{6,7}$ 6 Hz, $J_{6,5}$ ca. 4 Hz; C6-H_1; decouples at +222 Hz), ca. 4.37 (multiplet 1H, $J_{5,F}$ ca. 47 Hz, $J_{5,6}$ ca. 4 Hz, $J_{5,7}$? Hz; C5-H_1; decouples at +182 Hz), 4.05 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.07 (singlet, 3H; C6-CO-CH_3), 2.03 (singlet, 3H; CO-CH_3), 1.95-1.10 (multiplet, 6H; C2-H_2, C3-H_2, C4-H_2), 1.25 (multiplet, 3H, $J_{7,6}$ 6 Hz, $J_{7,F}$ 0.8 Hz; C7-H_3; decouples at -222 Hz). Found: C, 56.03; H, 8.15; F, 8.54. $C_{11}H_{19}F_1O_4$ requires: C, 56.41; H, 8.11; F, 8.11.

Rearrangement of trans-5,6-epoxyheptan-1-ol acetate (27) with BF_3-etherate in ether

The rearrangement of the epoxide (27) is carried out, in duplicate, under the same reaction conditions as that of cis-5,6-epoxyheptan-1-ol acetate (33). The crude produce is shown (g.l.c. using tetrahydrofurfuryl alcohol acetate as a standard) to contain: 5-acetoxy-2-methylpentanal (5%, 51), 7-acetoxyheptan-3-one (11%, 47), 7-acetoxyheptan-3-one (8%, 49), erythro-6-fluoro-5-hydroxyheptan-1-ol acetate (36%, 60) and erythro-5-fluoro-6-hydroxyheptan-1-ol acetate (35%, 63).

Isolation of reaction products from BF_3-etherate rearrangement of trans-5,6-epoxyheptan-1-ol acetate (27)

The epoxide (2 gm, 27) is rearranged and worked up in the usual way. The compounds in order of their elution from the preparative gas chromatography column are: 5-acetoxy-2-methylpentanal (51); n.m.r. δ 9.60 (doublet, 1H, $J_{CHO,2}$ 2 Hz;

CHO), 4.05 (poorly resolved triplet, 2H, $J_{5,4}$ 6 Hz; C5-H_2), 2.67-2.17 (multiplet, 1H; C2-H_1), 2.03 (singlet, 3H; Co-CH_3), 1.85-1.05 (multiplet, 6H; C2-H_2, C3-H_2, C4-H_2), 1.10 (doublet, 3H, $J_{CH_3,2}$ 6 Hz; C2-CH_3). The aldehyde decomposed rapidly on storage. 7-Acetoxyheptan-3-one (47) and 7-acetoxyheptan-2-one (49) are identical in all respects with the ketones from the rearrangement of cis-epoxyheptan-1-ol acetate (33). erythro-6-fluoro-5-hydroxyheptan-1-ol acetate (60); ν_{max} 3475, 1740, 1370, 1350 cm^{-1}; n.m.r. δ ca. 4.55 (multiplet, 1H, $J_{6,F}$ ca. 49 Hz, $J_{6,7}$ 6 Hz, $J_{6,5}$ 4 Hz; C6-H_1; decouples at +205 Hz and +182 Hz), 4.08 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), ca. 3.93 - ca. 3.50 (multiplet, 1H; C5-H_1), 2.03 (singlet, 3H; CO-CH_3), 1.83-1.22 (multiplet, 6H; C2-H_2, C3-H_2, C4-H_2), 1.30 (multiplet 3H, $J_{7,F}$ 25 Hz, $J_{7,6}$ 6 Hz; C7-H_3; decouples at -205 Hz and -182 Hz, i.e. $J_{6,F}$, $J_{7,5}$ are of the same sign). Found: C, 56.19; H, 8.90; F, 10.62. $C_9H_{17}O_3$ requires: C, 56.25; H, 8.85; F, 9.89. erythro-5-fluoro-6-hydroxyheptan-1-ol acetate (63); ν_{max} 3475, 1740, 1370, 1350 cm^{-1}; n.m.r. δ ca. 4.33 (multiplet, 1H, $J_{5,F}$ ca. 49 Hz?, $J_{5,6}$ ca. 5 Hz, $J_{5,4}$ ca. 6 Hz; C5-Hl; decouples at +170 Hz), 4.07 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), ca. 3.87 (multiplet, $J_{6,F}$ ca. 22 Hz, $J_{6,7}$ 6 Hz, $J_{6,5}$ ca. 4 Hz; C6-H_1; decouples at +160 Hz), 2.03 (singlet, 3 H; CO-CH_3), 2.10-1.00 (multiplet, 6H; C2-H_2, C3-H_2, C4-H_2), 1.20 (multiplet, 3H, $J_{7,6}$ 6 Hz, $J_{7,F}$ 1.2 Hz; C7-H_3; decouples at -160 Hz). Found: C, 55.91; H, 8.80; F, 10.31. $C_9H_{17}F_1O_3$ requires: C, 56.25; H, 8.85; F, 9.89.

Rearrangement of cis-4,5-epoxyhexan-1-ol acetate (31) with BF_3-etherate in ether

The rearrangement of the epoxide (31) is carried out, in duplicate, under similar reaction conditions to that of cis-5,6-epoxyheptan-1-ol acetate (33) except that in this case the internal standard is cyclohexanol. The crude product is shown (g.l.c. using cyclohexanol as a standard) to contain: erythro-2-(1-acetoxyethyl)tetrahydrofuran (30%, 37), 6-acetoxyhexan-3-one (30%, 48), 6-acetoxyhexan-2-one (14%, 50), threo-5-fluoro-4-hydroxyhexan-1-ol acetate (14%, 54) and threo-4-fluoro-5-hydroxyhexan-1-ol acetate (7%, 58).

Isolation of reaction products from BF_3-etherate rearrangement of cis-4,5-epoxyhexan-1-ol acetate (31)

The epoxide (1 gm, 31) is rearranged and worked up in the usual way. As both of the fluorohydrins (54,58) decompose during preparative gas chromatography they are converted to their acetates (55,59) first by reaction with acetyl chloride in pyridine. The pure compounds in order of their elution from the preparative gas chromatography column are: erythro-2-(1-acetoxyethyl)tetrahydrofuran (37); ν_{max} 1740, 1350 cm^{-1}; n.m.r. δ 4.90 (quartet of doublets, 1H, J_{H,CH_3} 6 Hz, J_{H_12} ca. 4.5 Hz; C2-methine), 4.07-3.60 (multiplet, 3H; C2-H_1, C5-H_2), 2.13-1.53 (multiplet, 4H; C3-H_2, C4-H_2), 2.03 (singlet, 3H; CO-CH_3), 1.22 (doublet 3H, $J_{CH_3,H}$ 6 Hz; COAC-CH_3). The alcohol obtained on reacting the acetate with $LiAlH_4$ in ether is identical in all respects to authentic erythro-2-(1-hydroxyethyl)tetrahydrofuran (36). 6-Acetoxyhexan-3-one (48); ν_{max} 1740, 1718, 1350 cm^{-1}; n.m.r. δ 4.07 (triplet, 3H, $J_{6,5}$ 6 Hz; C6-H_2), 2.50 (triplet, 2H, $J_{4,5}$ 6 Hz; C4-H_2), 2.45 (quartet, 2H, $J_{2,1}$ 7 Hz;

C_2-H_2; decouples at +83 Hz), 2.03 (singlet, 3H; CO-CH_3), 1.92 (quintet?, 2H, $J_{5,6}$ 6 Hz, $J_{5,4}$ 6 Hz; C5 H_2), 1.05 (triplet, 3H, $J_{1,2}$ 7 Hz; C1-H_3). Found: C, 60.84; H, 8.84. $C_8H_{14}O_3$ requires C, 60.76; H, 8.86. 6-Acetoxyhexan-2-one (50); ν_{max} 1740, 1720, 1350 cm^{-1}; n.m.r. δ 4.07 (poorly resolved triplet, 2H, $J_{6,5}$ 6 Hz; C6-H_2), 2.48 (poorly resolved triplet, 2H, $J_{3,4}$ 6 Hz; C3-H_2), 2.13 (singlet, 3H; C1-H_3), 2.03 (singlet, 3H; CO-CH_3), 1.77-1.48 (multiplet, 4H; C4-H_2, C5-H_2). Found: C, 60.80; H, 8.88. $C_8H_{14}O_3$ requires C, 60.76; H, 8.86. threo-4-Acetoxy-5-fluorohexan-1-ol acetate (55); ν_{max} 1740, 1350 cm^{-1}; n.m.r. δ 4.95 (multiplet, 1H, $J_{4,F}$ ca. 17 Hz, $J_{4,5}$ ca. 4 Hz, $J_{4,3}$? Hz; C4-H_1; decouples at ca. +181 Hz), 4.65 (multiplet, 1H, $J_{5,F}$ ca. 49 Hz, $J_{5,6}$ 6 Hz, $J_{5,4}$ ca. 4 Hz; C5-H_1; decouples at +213 Hz and +190 Hz), 4.08 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.10 (singlet, 3H; C4-CO-CH_3), 2.03 (singlet, 3H; CO-CH_3), 1.92-1.10 (multiplet, 4H; C2-H_2, C3-H_2), 1.30 (multiplet, 3H, $J_{6,5}$ 24 Hz, $J_{6,5}$ 6 Hz; C6-H_3; decouples at -213 Hz and -190 Hz, i.e. $J_{5,F}$, $J_{6,F}$ are of the same sign). Found: C, 54.13; H, 7.92; F, 8.81, $C_{10}H_{17}O_4$ requires: C, 54.55; H, 7.73, F, 8.64. threo-5-Acetoxy-6-fluorohexan-1-ol acetate (50); ν_{max} 1740, 1350 cm^{-1}; n.m.r. δ 5.02(multiplet, 1H, $J_{5,F}$ ca. 22 Hz, $J_{5,6}$ 6 Hz, $J_{5.4}$ ca. 4 Hz; C5-H_1; decouples at +222 Hz), ca. 4.35 (multiplet, 1H, $J_{4,F}$ ca. 47 Hz, $J_{4,5}$ ca. 4 Hz, $J_{4.3}$? Hz; C4-H_1; decouples at +182 Hz), 4.10 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.07 (singlet, 3H; C5-CO-CH_3), 2.03 (singlet, 3H; CO-CH_3), 2.00-1.10 (multiplet, 4H; C2-H_2, C3-H_2), 1.27 (doublet, 3H, $J_{6,5}$ 6 Hz; C6-H_3; decouples at -222 Hz). Found: C, 54.10,; H, 8.02; F, 9.13. $C_{10}H_{17}F_1O_4$ requires: C, 54.55; H, 7.73; F, 8.64.

Rearrangement of trans-4,5-epoxyhexan-1-ol acetate (25) with BF_3-etherate in ether

The rearrangement of the epoxide (25) is carried out, in duplicate, under similar reaction conditions to that of cis-4,5-epoxyhexan-1-ol acetate (31). The crude product is shown (g.l.c. using cyclohexanol as a standard) to contain: threo-2-(1-acetoxyethyl)tetrahydrofuran (62%, 39), 6-acetoxyhexan-3-one (ca. 3%, 48), 6-acetoxyhexan-2-one (trace, 50), erythro-5-fluoro-4-hydroxyhexan-1-ol acetate (17%, 61) and erythro-4-fluoro-5-hydroxyhexan-1-ol acetate (13%, 64).

Isolation of reaction products from BF_3-etherate rearrangement of trans-4,5-epoxyhexan-1-ol acetate (25)

The epoxide (2 gm, 25) is rearranged and worked up in the usual way. As both of the fluorohydrins (61,64) decompose during preparative gas chromatography they are converted to their acetates (62,65) first by reaction with acetyl chloride in pyridine. The pure compounds in order of their elution from the preparative gas chromatography column are: threo-2-(1-acetoxyethyl)tetrahydrofuran (39); ν_{max} 1735, 1350 cm^{-1}; n.m.r. δ 4.85 (quintet, 1H, $J_{H,2}$ 6 Hz, J_{H,CH_3} 6 Hz; C2-methine), 4.05-3.58 (multiplet, 3H; C2-H_1, C5-H_2), 2.25-1.50 (multiplet, 4H; C3-H_2, C4-H_2), 2.05 (singlet, 3H; CO-CH_3), 1.20 (doublet, 3H, $J_{CH_3,H}$ 6 Hz; COAc-CH_3). The alcohol obtained on reacting the acetate with $LiAlH_4$ in ether is identical in all respects to authentic threo-2-(1-hydroxyethyl)tetrahydrofuran (38). erythro-4-Acetoxy-5-fluorohexan-1-ol acetate (62); ν_{max} 1740, 1350 cm^{-1}, n.m.r. δ 4.91 (multiplet, 1H, $J_{4,F}$ ca. 17 Hz, $J_{4,5}$ ca. 4 Hz, $J_{4,3}$? Hz; C4-H_1; decouples at +184 Hz), 4.67 (multiplet 1H, $J_{5,F}$ ca. 49 Hz, $J_{5,6}$ 6 Hz, $J_{5,4}$ ca. 4 Hz; C5-H_1;

decouples at +213 Hz and +189 Hz), 4.08 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.08 (singlet, 3H; C4-CO-CH_3), 2.03 (singlet, 3H; CO-CH_3), 1.80-1.42 (multiplet, 4H; C2-H_2), 1.32 (multiplet, 3H, $J_{6,F}$ 24 Hz, $J_{6,5}$ 6 Hz; C6-H_3; decouples at -213 Hz and -189 Hz, i.e. $J_{5,F}$, $J_{6,F}$ are of the same sign). Found: C, 54.63; H, 7.42; F, 8.12. $C_{10}H_{17}F_1O_4$ requires: C, 54.55; H, 7.73; F, 8.64. erythro-5-Acetoxy-4-fluorohexan-1-ol acetate (65); ν_{max} 1740, 1355 cm^{-1}; n.m.r. δ 4.95 (multiplet 1H, $J_{5,F}$ ca. 19 Hz, $J_{5,6}$ 6 Hz, $J_{5,4}$ ca. 4 Hz; C5-H_1; decouples at +223 Hz), ca. 4.45 (multiplet, 1H, $J_{4,5}$ ca. 49 Hz, $J_{4,5}$ ca. 4 Hz, $J_{4,3}$? Hz; C4-H_1; decouples at ca. +177Hz), 4.10 (poorly resolved triplet, 2H, $J_{1,2}$ 6 Hz; C1-H_2), 2.07 (singlet, 3H; C5-CO-CH_3), 2.03 (singlet, 3H; CO-CH_3), 1.97-0.92 (multiplet, 4H; C2-H_2, C3-H_2), 1.25 (multiplet, 3H, $J_{6,5}$ 6 Hz, $J_{6,F}$ 1.2 Hz; C6-H_3; decouples at -223 Hz). Found: C, 55.01; H, 7.98; F, 8.97. $C_{10}H_{17}F_1O_4$ requires: C, 54.55; H, 7.73; F, 8.64.

Rearrangement of cis-3,4-epoxypentan-1-ol acetate (29) with BF_3-etherate in ether

The rearrangement of the epoxide (29) is carried out in duplicate. To two oven dried conical flasks sodium dried ether (120 ml, 100 ml) and epoxide (29) (120.1 mg, 97.7 mg) are added. The mixtures are stirred with a magnetic stirrer and BF_3-etherate (430 mg, 360 mg) added. The reactions are allowed to proceed for two and one half hours at room temperature and then quenched with saturated potassium carbonate solution (0.5 ml, 0.5 ml). After a further fifteen minutes' stirring tetrahydrofurfuryl alcohol acetate (118.2 mg, 112.7 mg) and anhydrous potassium carbonate are added. The solids are

removed by filtration and the ether by careful distillation. The crude product is shown (g.l.c. using the tetrahydrofurfuryl alcohol acetate as a standard) to contain: trans-2-methyltetrahydrofuran-3-ol acetate (40%, 43) and traces of two compounds that have the characteristic retention times of ketone products. No other low retention time products and no products with retention times characteristic of fluorohydrins are found.

trans-2-Methyltetrahydrofuran-3-ol acetate (43)

The epoxide (0.5 gm, 29) is rearranged and worked up in the usual way. The major product trans-2-methyltetrahydrofuran-3-ol acetate is purified by preparative gas chromatography; ν_{max} 1735, 1365, 1350 cm^{-1}; n.m.r. δ 4.97-4.73 (multiplet, 1H; C3-H_1), 4.15-3.70 (multiplet, 3H; C2-H_1, C5-H_2), 2.57-1.83 (multiplet, 2H; C4-H_2), 2.03 (singlet, 3H; CO-CH_3), 1.22 (doublet, 3H, $J_{CH_3,2}$ 6 Hz; C2-methyl). Found: C, 58.12; H, 8.30. $C_7H_{12}O_3$ requires C, 58.33; H, 8.33. The alcohol obtained on reacting the acetate with $LiAlH_4$ in ether is identical in all respects to authentic trans-2-methyltetrahydrofuran-3-ol (42).

Rearrangement of trans-3,4-epoxypentan-1-ol acetate (23) with BF_3-etherate in ether

The rearrangement of the epoxide (23) is carried out, in duplicate, under the same reaction conditions as that of cis-3,4-epoxypentan-1-ol acetate (29). The crude product is shown (g.l.c. using tetrahydrofurfuryl alcohol acetate as a standard) to contain: cis-2-methyltetrahydrofuran-3-ol acetate (68%, 46) and traces of three compounds that have the characteristic retention times of ketone products. The retention time of the

last "ketone", from the rearrangement of trans-3,4-epoxypentan-1-ol acetate is the same as the retention time of the first "ketone", from the rearrangement of cis-3,4-epoxypentan-1-ol acetate. No other products have the same retention times. No other low retention time products and no products with retention times characteristic of fluorohydrins are found.

cis-2-Methyltetrahydrofuran-3-ol acetate (46)

The epoxide (1 gm, 23) is rearranged and worked up in the usual way. The major product cis-2-methyltetrahydrofuran-3-ol acetate is purified by preparative gas chromatography; ν_{max} 1740, 1360 cm^{-1}; n.m.r. δ 5.40-5.18 (multiplet, 1H; C3-H_1), 4.25-3.52 (multiplet, 3H; C2-H_1, C5-H_2), 2.67-1.67 (multiplet, 2H; C4-H_2), 2.07 (singlet, 3H; CO-CH_3), 1.20 (doublet, 3H, $J_{CH_3,2}$ 6 Hz; C2-methyl). Found: C, 58.20; H, 8.30. $C_7H_{12}O_3$ requires C, 58.33; H, 8.33. The alcohol obtained on reacting the acetate with $LiAlH_4$ in ether is identical in all respects to authentic cis-2-methyltetrahydrofuran-3-ols (45).

Rearrangement of cis-3,4-epoxypentan-1-ol acetate (29) with toluene-p-sulphonic acid in ether

The rearrangement fo the epoxide (29) is carried out in a similar fashion to the BF_3-etherate reactions but using an equivalent amount of toluene-p-sulphonic acid (4.7 gm/l), that has been dried by azeotropic distillation with benzene, instead of the Lewis acid. The reaction is worked up in the usual manner and the crude product is shown (g.l.c.) to contain: trans-2-methyltetrahydrofuran-3-ol acetate (65%, 43), cis-2-methyltetrahydrofuran-3-ol acetate (25%, 46) and two unknown products (6%, 6%).

Rearrangement of trans-3,4-epoxypentan-1-ol acetate (23) with toluene-p-sulphonic acid in ether

The rearrangement of the epoxide (23) with toluene-p-sulphonic acid is carried out in a similar fashion to that of cis-3,4-epoxypentan-1-ol acetate (29). The crude product is shown (g.l.c.) to contain: trans-2-methyltetrahydrofuran-3-ol acetate (10%, 43), cis-2-methyltetrahydrofuran-3-ol acetate (80%, 46) and two unknown products (6%, 4%).

Rearrangement of cis-3,4-epoxypentan-1-ol acetate (29) with trifluoroacetic acid in ether

The rearrangement of the epoxide (29) is carried out in a similar fashion to the BF_3-etherate reactions but using an equivalent amount of trifluoroacetic acid (2.9 gm/l) instead of the Lewis acid. The reaction is worked up in the usual manner and the crude product is shown (g.l.c.) to contain: trans-2-methyltetrahydrofuran-3-ol acetate (97%, 43) and a trace of cis-2-methyltetrahydrofuran-3-ol acetate (46).

Rearrangement of trans-3,4-epoxypentan-1-ol acetate (23) with trifluoroacetic acid in ether

The rearrangement of the epoxide (23) with trifluoroacetic acid is carried out in a similar fashion to that of cis-3,4-epoxypentan-1-ol acetate (29). The crude product is shown (g.l.c.) to contain: trans-2-methyltetrahydrofuran-3-ol acetate (5%, 43) and cis-2-methyltetrahydrofuran-3-ol acetate (95%, 46).

Synthesis and rearrangement of ^{18}O trans-3,4-epoxypentan-1-ol acetate (23)

To an oven dried conical flask dry pyridine (2 ml) and trans-pent-3-en-1-ol (250 mg, 7) are added. The contents of

the flask are stirred and acetyl chloride (28% ^{18}O, 230 mg) is cautiously added. The mixture is left at room temperature overnight and the next day the acetate (6) is extracted with ether and washed with 10% hydrochloric acid. The ether extract is dried (potassium carbonate) and the solvent removed by careful distillation. The crude acetate (6) is then reacted with monoperoxyphthalic acid (20 ml, 0.35 M) at 5°C for nine days after which the phthalic acid that has precipitated out is removed by filtration. The remaining acid in the ether solution is removed by overnight reaction with anhydrous potassium carbonate (1 gm). The next day the solids are removed by filtration and the ether by careful distillation. The crude ^{18}O trans-3,4-epoxypentan-1-ol acetate is then dissolved in sodium dried ether (300 ml) and rearranged with BF_3-etherate in the usual manner. After work up the ^{18}O cis-2-methyltetrahydrofuran-3-ol acetate (46) is purified by preparative gas chromatography.

The pure ^{18}O acetate (46) is dissolved in sodium dried ether (50 ml) an excess of $LiAlH_4$ is added and the mixture refluxed for two hours. The $LiAlH_4$ is broken down by addition of hydrated sodium sulphate and the solids removed by filtration. After the ether has been removed by distillation the ^{18}O cis-2-methyltetrahydrofuran-3-ol (45) is purified by preparative gas chromatography.

Mass spectra results of ^{18}O enriched cis-2-methyltetrahydrofuran-3-ol acetate (46) and cis-2-methyltetrahydrofuran-3-ol (45)

When the mass spectrum of the ^{18}O enriched acetate (46) is run the ratio of the parent plus two, to the parent ion is 0.287. This ratio is reduced to 0.278 when the correction for the natural abundance of the $m^+ + 2$ peak is made. This result

is also checked on the M^++2-methyl and M^+-methyl peaks, because of the weak intensities of the molecule ions, and a corrected ratio of 0.279 is obtained.

The corrected ratio for the molecule ions of alcohol (45) is found to be 0.256.

Synthesis and rearrangement of ^{18}O trans-4,5-epoxyhexan-1-ol acetate (25)

The synthesis and rearrangement of ^{18}O trans-4,5-epoxyhexan-1-ol acetate are carried out in a similar manner to that for ^{18}O trans-3,4-epoxypentan-1-ol acetate (23). In this case the major product is ^{18}O threo-2-(1-acetoxyethyl)tetrahydrofuran (39) and it is converted to the corresponding alcohol (38) with $LiAlH_4$ in a similar fashion to ^{18}O cis-2-methyltetrahydrofuran-3-ol acetate (46).

Mass spectra results of ^{18}O enriched threo-2-(1-acetoxyethyl)-tetrahydrofuran (39) and threo-2-(1-hydroxyethyl)tetrahydrofuran (38)

When the mass spectrum of the ^{18}O enriched acetate (39) is run the ratio of the parent plus two, to the parent ion is 0.281. This ratio is reduced to 0.271 when the correction for the natural abundance of the M^++2 is made.

The mass spectrum of the alcohol (45) obtained from the ^{18}O acetate shows no isotope enrichment.

Reaction of cis-5,6-epoxyheptan-1-ol acetate (33) with potassium tert-butoxide in tert-butanol

A solution of potassium tert-butoxide (1M) is made by refluxing potassium (80 mg) with dry tert-butanol (2 ml) until all the metal has dissolved. The apparatus used is flamed and

flushed with dry nitrogen while the tert-butanol is dried by distillation off sodium.

cis-5,6-Epoxyheptan-1-ol acetate (100 mg, 33) in tert-butanol (0.5 ml) is added to the potassium tert-butoxide solution and the mixture refluxed for one half hour. After cooling sodium dried ether (25 ml) and sodium bicarbonate (200 mg) are added and the mixture stirred for one half hour. The solids are removed by filtration and the ether by distillation. The crude product is shown (g.l.c.) to contain only threo-2-(1-hydroxyethyl)tetrahydropyran (35).

Reaction of trans-5,6-epoxyheptan-1-ol acetate (27) with potassium tert-butoxide in tert-butanol

The rearrangement of the epoxide (27) is carried out under the same reaction conditions as that of cis-5,6-epoxyheptan-1-ol acetate (33). The crude product is shown (g.l.c.) to contain: erythro-2-(1-hydroxyethyl)tetrahydropyran (97%, 34) and an unknown product (ca. 3%).

Reaction of threo-5-acetoxy-6-fluoroheptan-1-ol acetate (53) and threo-6-acetoxy-5-fluoroheptan-1-ol acetate (57) with potassium tert-butoxide in tert-butanol

The rearrangement of the fluorine diacetate isomers (53,57) is carried out under the same reaction conditions as that of cis-5,6-epoxyheptan-1-ol acetate (33). In both cases the crude products are shown (g.l.c.) to contain only threo-2-(1-hydroxyethyl)tetrahydropyran (35).

Reaction of erythro-6-fluoro-5-hydroxyheptan-1-ol acetate (60) and erythro-5-fluoro-6-hydroxyheptan-1-ol acetate (63) with potassium tert-butoxide in tert-butanol

The rearrangement of the fluorohydrin monoacetate isomers (60,63) is carried out under the same reaction conditions as that of cis-5,6-epoxyheptan-1-ol acetate (33). In both cases the crude products are shown (g.l.c.) to contain: erythro-2-(1-hydroxyethyl)tetrahydropyran (97%, 34) and an unknown product (ca. 3%) with the same retention time as the unknown from the rearrangement of trans-5,6-epoxyheptan-1-ol acetate (27).

Reaction of cis-4,5-epoxyhexan-1-ol acetate (31) with potassium tert-butoxide in tert-butanol

The rearrangement of the epoxide (31) is carried out under the same reaction conditions as that of cis-5,6-epoxyheptan-1-ol acetate (33). The crude product is shown (g.l.c.) to contain only threo-2-(1-hydroxyethyl)tetrahydrofuran (38).

Reaction of trans-4,5-epoxyhexan-1-ol acetate (25) with potassium tert-butoxide in tert-butanol

The rearrangement of the epoxide (25) is carried out under the same reaction conditions as that of cis-5,6-epoxyheptan-1-ol acetate (33). The crude product is shown (g.l.c.) to contain: erythro-2-(1-hydroxyethyl)tetrahydrofuran (97%, 36) and trans-2-methyltetrahydropyran-3-ol (3%, 40).

Reaction of threo-4-acetoxy-5-fluorohexan-1-ol acetate (55) and threo-5-acetoxy-4-fluorohexan-1-ol acetate (59) with potassium tert-butoxide in tert-butanol

The rearrangement of the fluorine diacetate isomers (55, 59) is carried out under the same reaction conditions as that of cis-5,6-epoxyheptan-1-ol (33). In both cases the crude products are shown (g.l.c.) to contain only threo-2-(1-hydroxyethyl)tetrahydrofuran (38).

Reaction of erythro-4-acetoxy-5-fluorohexan-1-ol acetate (62) and erythro-5-acetoxy-4-fluorohexan-1-ol acetate (65) with potassium tert-butoxide in tert-butanol

The rearrangement of the fluorine diacetate isomers (62, 65) is carried out under the same reaction conditions as that of cis-5,6-epoxyheptan-1-ol acetate (33). In the case of erythro-4-acetoxy-5-fluorohexan-1-ol acetate the crude product is shown (g.l.c.) to contain: erythro-2-(1-hydroxyethyl)tetrahydrofuran (97%, 36) and trans-2-methyltetrahydropyran-3-ol (ca. 3%, 40). However, in the case of erythro-5-acetoxy-4-fluorohexan-1-ol acetate the crude product is shown (g.l.c.) to contain: threo-2-(1-hydroxyethyl)tetrahydrofuran (5%, 38), erythro-2-(1-hydroxyethyl)tetrahydrofuran (92%), and trans-2-methyltetrahydropyran-3-ol (ca. 3%).

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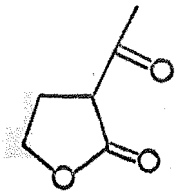

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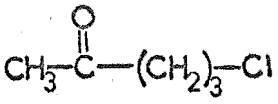

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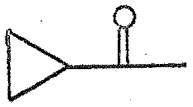

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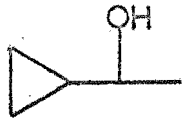

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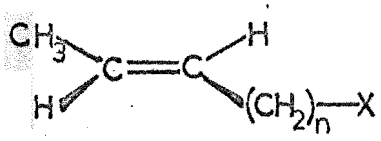

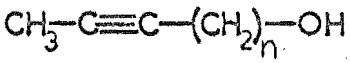

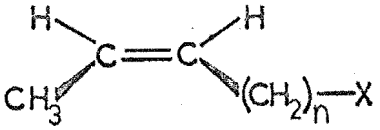

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6 n=2, X=OAc
7 n=2, X=OH
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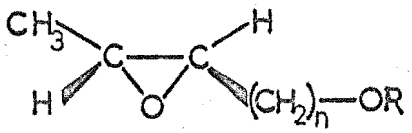
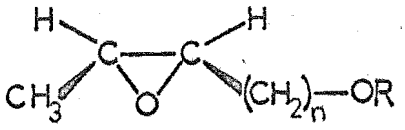
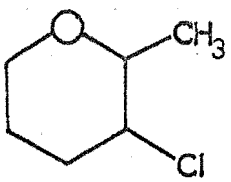
9 n=3, X=OH
10 n=4, X=OAc
11 n=4, X=OH

12 n=2
13 n=3
14 n=4

15 n=2, X=OAc
16 n=2, X=OH
17 n=3, X=OAc
18 n=3, X=OH
19 n=4, X=OAc
20 n=4, X=OH







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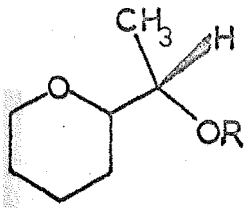
22 n=2, R=H
23 n=2, R=Ac
24 n=3, R=H
25 n=3, R=Ac
26 n=4, R=H
27 n=4, R=Ac

28 n=2, R=H
29 n=2, R=Ac
30 n=3, R=H
31 n=3, R=Ac
32 n=4, R=H
33 n=4, R=Ac



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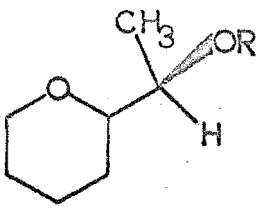

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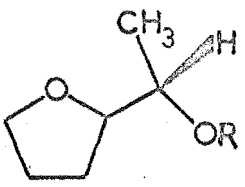

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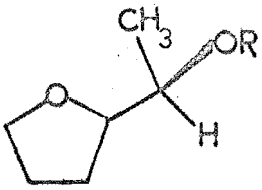

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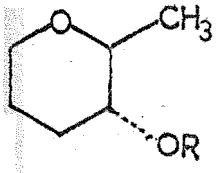

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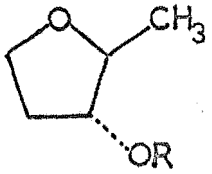

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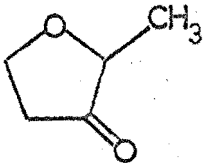

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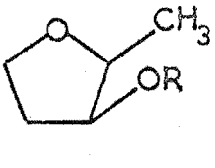

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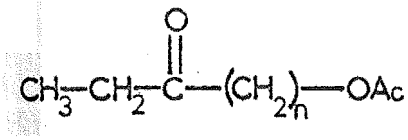

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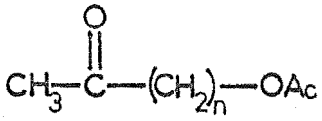
48 n = 3



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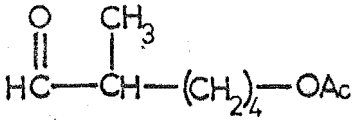

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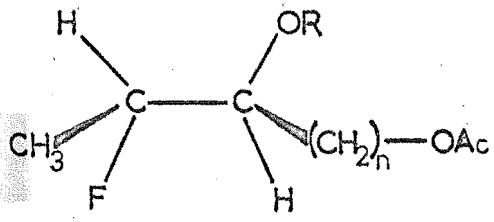

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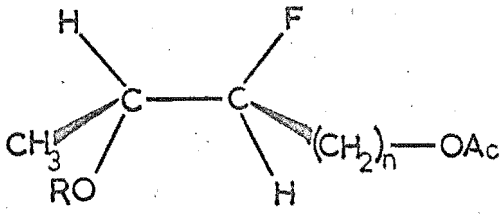
53 n = 4, R = Ac

54 n = 3, R = H

55 n = 3, R = Ac



56 n = 4, R = H

57 n = 4, R = Ac

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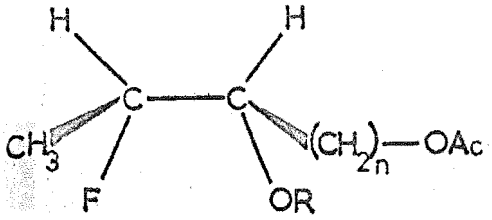
59 n = 3, R = Ac



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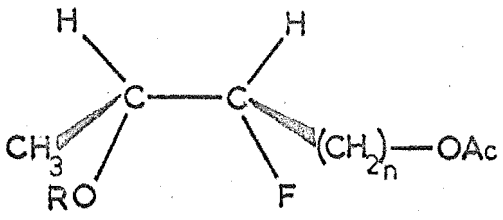
61 n = 3, R = H

62 n = 3, R = Ac



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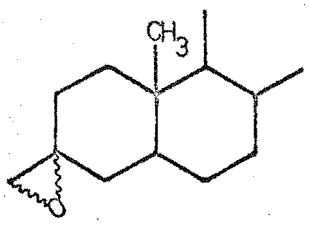
64 n = 3, R = H

65 n = 3, R = Ac



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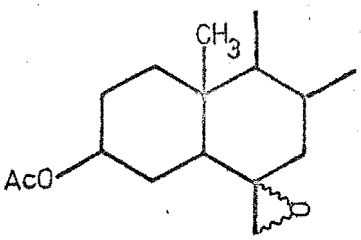

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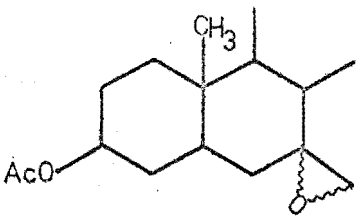

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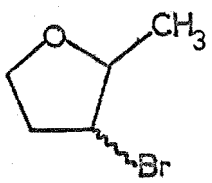

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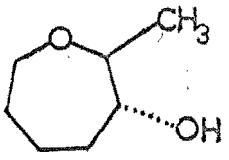

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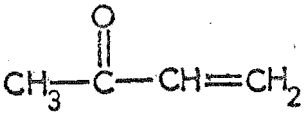

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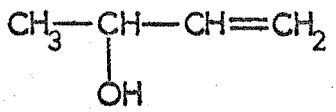

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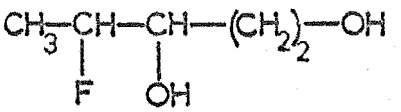

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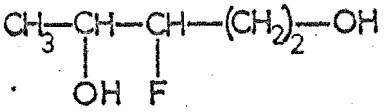

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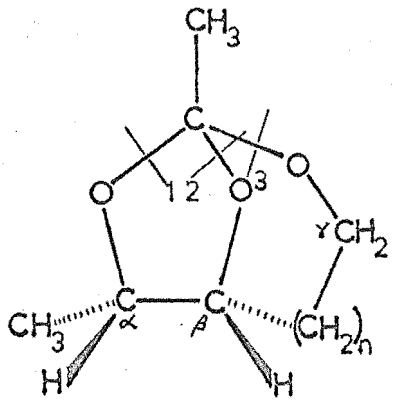

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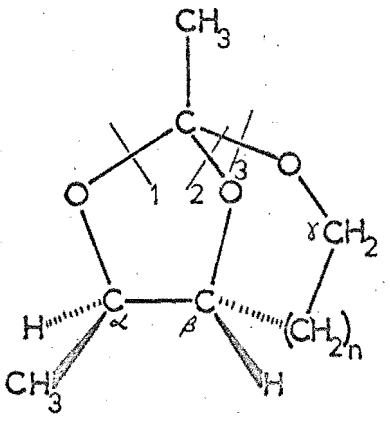

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